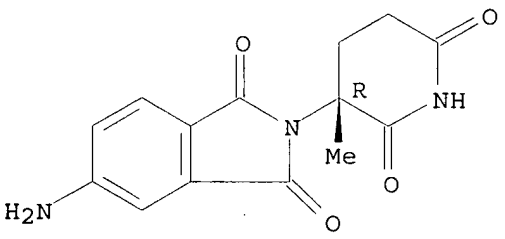
```
=> d his

     (FILE 'HOME' ENTERED AT 17:14:40 ON 06 DEC 2002)

     FILE 'REGISTRY' ENTERED AT 17:14:53 ON 06 DEC 2002
L1                STRUC
L2             10 S L1
L3            175 S L1 FUL
L4                STRUC
L5            166 SEARCH L4 SSS  SUB=L3 FUL

     FILE 'CAPLUS' ENTERED AT 17:20:41 ON 06 DEC 2002
L6             17 S L5

     FILE 'REGISTRY' ENTERED AT 17:21:25 ON 06 DEC 2002

=> s l3 not l5
L7              9 L3 NOT L5
```

=> s l7
L8 8 L7

=> d bib abs hitstr 1-8

L8 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 2002:211227 CAPLUS
DN 137:241664
TI Thalidomide and its analogues as cyclooxygenase inhibitors
AU Noguchi, Tomomi; Shimazawa, Rumiko; Nagasawa, Kazuo; Hashimoto, Yuichi
CS Institute of Molecular & Cellular Biosciences, The University of Tokyo, Bunkyo-ku, Tokyo, 113-0032, Japan
SO Bioorganic & Medicinal Chemistry Letters (2002), 12(7), 1043-1046
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB Thalidomide showed cyclooxygenase (COX)-1/2 inhibitory activity with a potency comparable to that of aspirin. Structural development studies of thalidomide resulted in potent COX-1/2 inhibitors, and COX-1-selective and COX-2-selective inhibitors.
IT **212394-10-0**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide and analogs as cyclooxygenase inhibitors)
RN 212394-10-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1999:603139 CAPLUS
DN 131:214197
TI Preparation of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines for reducing inflammatory cytokine levels.
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu; Man, Hon-wah
PA Celgene Corp., USA
SO U.S., 12 pp., Cont. -in-part of U. S. 5,874,448.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

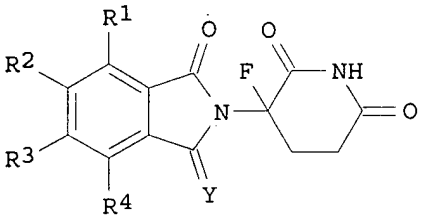
	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5955476	A	19990921	US 1998-42274	19980313
	US 5874448	A	19990223	US 1997-976140	19971118
	CA 2317834	AA	19990916	CA 1998-2317834	19981117
	WO 9946258	A1	19990916	WO 1998-US24453	19981117

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 9914138	A1	19990927	AU 1999-14138	19981117	
AU 752958	B2	20021003			
EP 1062214	A1	20001227	EP 1998-958016	19981117	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
JP 2002506068	T2	20020226	JP 2000-535637	19981117	
BR 9815613	A	20020528	BR 1998-15613	19981117	
NO 2000002529	A	20000630	NO 2000-2529	20000516	
FI 2000001192	A	20000714	FI 2000-1192	20000518	
PRAI US 1997-976140	A2	19971118			
US 1998-42274	A	19980313			
WO 1998-US24453	W	19981117			

OS MARPAT 131:214197

GI



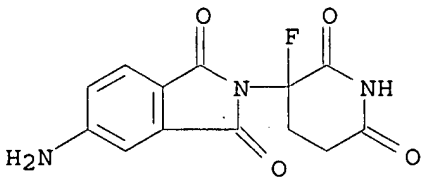
I

AB Title compds. (I; Y = O, H2; R1-R4 = H, halo, alkyl, alkoxy, amino), were prepd. for redn. of tumor necrosis factor and interleukin levels (no data). Thus, a soln. of 1,3-dioxo-2-(1-tert-butoxycarbonyl-2,6-dioxopiperidin-3-yl)isoindoline (prepn. given) in THF at -40.degree. was treated with Li[N(SiMe3)]2 soln. and then with N-fluorobenzenesulfonimide followed by stirring overnight to give 10% 1,3-dioxo-2-(1-tert-butoxycarbonyl-2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline. The latter was stirred with HCl in dioxane for 3 days to give 77% 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline. Drug formulations contg. the latter are given.

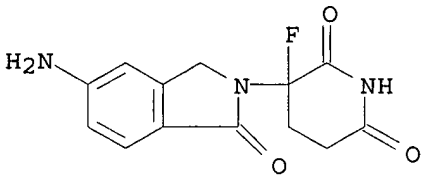
IT **220460-57-1 220460-62-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines for reducing inflammatory cytokine levels)

RN 220460-57-1 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)



RN 220460-62-8 CAPLUS
CN 2,6-Piperidinedione, 3-(5-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-3-fluoro- (9CI) (CA INDEX NAME)

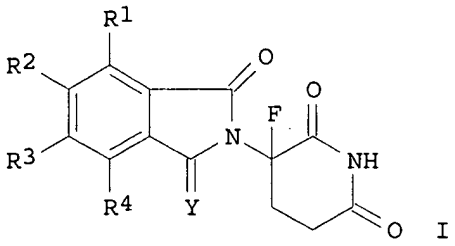


RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1999:595162 CAPLUS
DN 131:228653
TI Preparation of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and their use to reduce tumor necrosis factor .alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu; Man, Hon-wah
PA Celgene Corporation, USA
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9946258	A1	19990916	WO 1998-US24453	19981117
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 5955476	A	19990921	US 1998-42274	19980313
	CA 2317834	AA	19990916	CA 1998-2317834	19981117
	AU 9914138	A1	19990927	AU 1999-14138	19981117
	AU 752958	B2	20021003		
	EP 1062214	A1	20001227	EP 1998-958016	19981117
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002506068	T2	20020226	JP 2000-535637	19981117
	BR 9815613	A	20020528	BR 1998-15613	19981117
	NO 2000002529	A	20000630	NO 2000-2529	20000516
	FI 2000001192	A	20000714	FI 2000-1192	20000518
PRAI	US 1998-42274	A	19980313		
	US 1997-976140	A2	19971118		
	WO 1998-US24453	W	19981117		

OS MARPAT 131:228653
GI



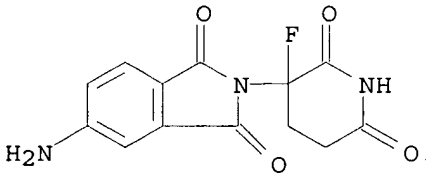
I

AB 1-Oxo- and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines (I; R1-R4 = H, halo, C1-4 alkyl, C1-4 alkoxy, amino; Y = O, H2) and their acid addn. salts reduce the levels of inflammatory cytokines, e.g., TNF-.alpha. in mammals (no data). A typical embodiment is 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline which was prepd. by N-protection of 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)isoindoline with (Me3CO2C)2O (90%), fluorination of N-BOC-protected intermediate with (PhSO2)2NF in presence of BuLi or (Me3Si)2NLi (10%), and deprotection with HCl (dioxane soln.) (77% yield). Tablets, capsules and injection or infusion solns. contg. I are formulated.

IT **220460-57-1P 220460-62-8P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and their use to reduce tumor necrosis factor .alpha. levels)

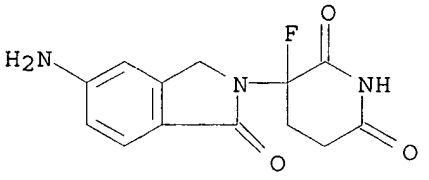
RN 220460-57-1 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



RN 220460-62-8 CAPLUS

CN 2,6-Piperidinedione, 3-(5-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-3-fluoro- (9CI) (CA INDEX NAME)

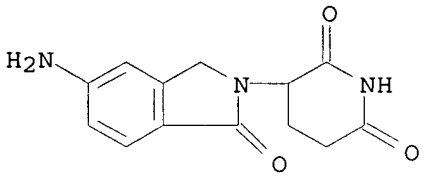


RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

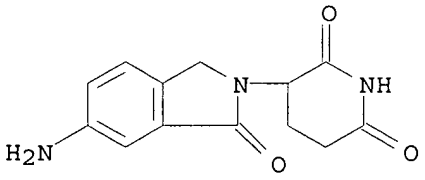
L8 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2002 ACS

AN 1999:386135 CAPLUS

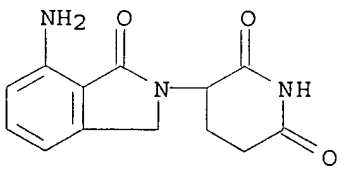
DN 131:129881
TI Amino-substituted thalidomide analogs: potent inhibitors of TNF-.alpha. production
AU Muller, George W.; Chen, Roger; Huang, Shaei-Yun; Corral, Laura G.; Wong, Lu Min; Patterson, Rebecca T.; Chen, Yuxi; Kaplan, Gilla; Stirling, David I.
CS Celgene Corporation, Warren, NJ, 07059, USA
SO Bioorganic & Medicinal Chemistry Letters (1999), 9(11), 1625-1630
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB Thalidomide is a known inhibitor of TNF-.alpha. release in LPS stimulated human PBMC. Herein we describe the TNF-.alpha. inhibitory activity of amino substituted analogs of thalidomide and its isoindolin-1-one analog, EM-12. The 4-amino substituted analogs were found to be potent inhibitors of TNF-.alpha. release in LPS stimulated human PBMC.
IT **191732-70-4P 191732-74-8P 191732-75-9P**
191732-76-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(amino derivs. of thalidomide and EM-12 as inhibitors of TNF-.alpha. prodn.)
RN 191732-70-4 CAPLUS
CN 2,6-Piperidinedione, 3-(5-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



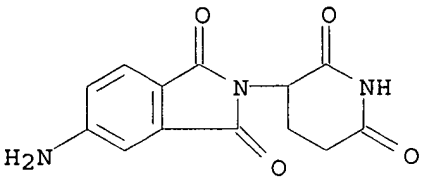
RN 191732-74-8 CAPLUS
CN 2,6-Piperidinedione, 3-(6-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



RN 191732-75-9 CAPLUS
CN 2,6-Piperidinedione, 3-(7-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



RN 191732-76-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)

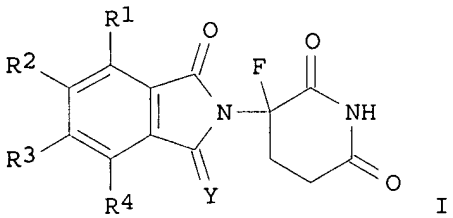


RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1999:136769 CAPLUS
DN 130:168244
TI Substituted 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and method of reducing TNF.alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-Chu; Man, Hon-Wah
PA Celgene Corporation, USA
SO U.S., 10 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5874448	A	19990223	US 1997-976140	19971118
	US 5955476	A	19990921	US 1998-42274	19980313
	NO 2000002529	A	20000630	NO 2000-2529	20000516
	FI 2000001192	A	20000714	FI 2000-1192	20000518
PRAI	US 1997-976140	A2	19971118		
	US 1998-42274	A	19980313		
	WO 1998-US24453	W	19981117		

OS MARPAT 130:168244
GI

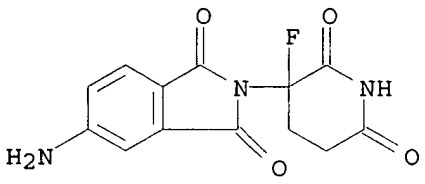


I

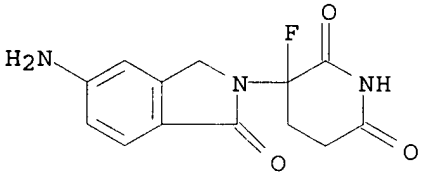
AB 1-Oxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines reduce the levels of TNF.alpha. in mammals (no data), and may be useful in the treatment of viral infections. The compds. I [Y = O or H2; R1, R2, R3, and R4 = H, halo, C1-4 alkyl or alkoxy, or amino], and their acid addn. salts when a protonatable N atom is present, are claimed. A typical embodiment is 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline (II), i.e. I [Y = O, R1-R4 = H]. This compd. was prepd. in a variety of ways. For instance, the non-fluorinated analog of II was N-BOC-protected on its piperidine ring, lithiated with BuLi in THF, fluorinated with N-fluorobenzenesulfonimide, and deprotected with HCl, to give II.

IT **220460-57-1P**, 1,3-Dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)-5-aminoisoindoline **220460-62-8P**, 1-Oxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)-5-aminoisoindoline **220460-76-4P**, 1,3-Dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)-5-aminoisoindoline hydrochloride
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compd.; prepn. of substituted (dioxofluoropiperidinyl)isoindolines and method of reducing TNF.alpha. levels)

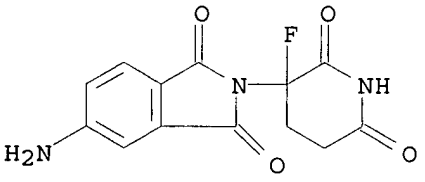
RN 220460-57-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-(9CI) (CA INDEX NAME)



RN 220460-62-8 CAPLUS
CN 2,6-Piperidinedione, 3-(5-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)-3-fluoro- (9CI) (CA INDEX NAME)



RN 220460-76-4 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(3-fluoro-2,6-dioxo-3-piperidinyl)-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1998:486299 CAPLUS
DN 129:216494
TI Tumor necrosis factor-alpha production enhancing activity of substituted 3'-methylthalidomide: influence of substituents at the phthaloyl moiety on the activity and stereoselectivity
AU Miyachi, Hiroyuki; Kolso, Yukiko; Shirai, Ryuichi; Niwayama, Satomi; Liu,

Jun O.; Hashimoto, Yuichi

CS Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, 113-0032, Japan

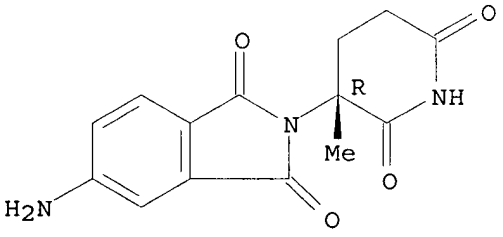
SO Chemical & Pharmaceutical Bulletin (1998), 46(7), 1165-1168
CODEN: CPBTAL; ISSN: 0009-2363
PB Pharmaceutical Society of Japan
DT Journal
LA English
OS CASREACT 129:216494

AB The synthesis and tumor necrosis factor (TNF)-.alpha. prodn. enhancing activity of substituted 3'-methyl-thalidomides on human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate (TPA) was described. Though the introduction of an electron-donating amino group at the phthaloyl moiety of .alpha.-methylthalidomides enhanced the activity, substituted .alpha.-methylthalidomides showed decreased stereoselectivity as compared to that of non-substituted .alpha.-methylthalidomide. The data indicates that the TNF-.alpha. prodn. enhancing activity of thalidomide derivs. depends on both the electronic-state of substituents at the fused benzene ring and the stereochem. of the glutarimide moiety. (S)-4-amino-3'-methylthalidomide induced a 695% increase in the amt. of tumor necrosis factor-alpha prodn. at 0.3.mu.m by the human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate.

IT **212394-10-0P 212394-11-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tumor necrosis factor-alpha prodn. enhancing activity of substituted 3'-methylthalidomides)

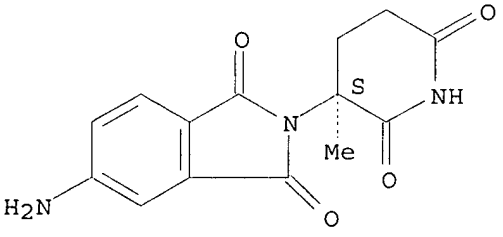
RN 212394-10-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 212394-11-1 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-[(3S)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

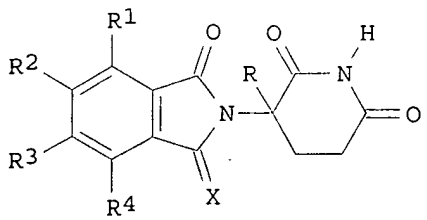


RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

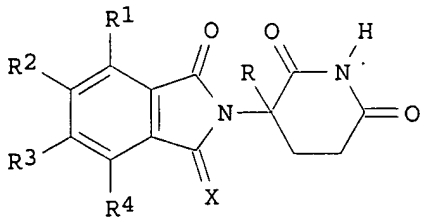
L8 ANSWER 7 OF 8 CAPLUS COPYRIGHT 2002 ACS
AN 1998:87727 CAPLUS
DN 128:140615
TI Substituted 2-(2,6-dioxo-3-piperidinyl)phthalimides and -1-oxoisoindolines and method of reducing TNF-.alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu
PA Celgene Corp., USA; Muller, George W.; Stirling, David I.; Chen, Roger Shen-Chu
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9803502	A1	19980129	WO 1997-US13375	19970724
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5635517	A	19970603	US 1996-690258	19960724
	US 5635517	B1	19990629		
	US 5798368	A	19980825	US 1996-701494	19960822
	AU 9738998	A1	19980210	AU 1997-38998	19970724
	AU 715779	B2	20000210		
	EP 925294	A1	19990630	EP 1997-936295	19970724
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2001503384	T2	20010313	JP 1998-507259	19970724
	RU 2177944	C2	20020110	RU 1999-103124	19970724
	FI 9900101	A	19990319	FI 1999-101	19990119
	US 6281230	B1	20010828	US 2000-543809	20000406
	US 6476052	B1	20021105	US 2000-633908	20000807
	US 6316471	B1	20011113	US 2000-634061	20001017
	US 6335349	B1	20020101	US 2000-716528	20001120
	US 2002045643	A1	20020418	US 2001-781179	20010212
	US 2002183360	A1	20021205	US 2002-119486	20020410
PRAI	US 1996-690258	A	19960724		
	US 1996-701494	A	19960822		
	WO 1994-US7411	A	19940701		
	US 1996-701499	A1	19960724		
	US 1997-48278P	P	19970530		
	WO 1997-US13375	W	19970724		
	US 1999-230389	B3	19990507		
	US 2000-543804	A3	20000406		
	US 2000-543809	A1	20000406		
	US 2000-633908	A1	20000807		

OS MARPAT 128:140615
GI



I



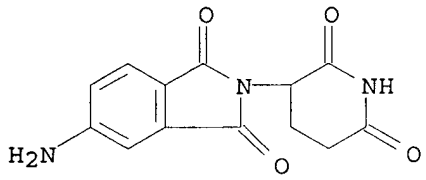
I

AB Title compds. I (X = O, H2; R = H, alkyl, benzyl, halo; R1, R2, R3, R4 = H, alkyl, alkoxy, halo, amino) were prepd. for TNF-.alpha. redn. in mammals. Thus, I (X = O, R = R1 = R3 = R4 = H, R2 = NO2), prepd. from 4-nitrophthalic anhydride and .alpha.-aminoglutarimide hydrochloride, was hydrogenated over 10% Pd/C in 1,4-dioxane at 50 psi for 6.5 h to give 69% I (X = O, R = R1 = R3 = R4 = H, R2 = NH2). Several examples of formulations were given.

IT **191732-76-0P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(2-(2,6-dioxo-3-piperidinyl)phthalimides and -1-oxoisoindolines for reducing TNF-.alpha. levels)

RN 191732-76-0 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



L8 ANSWER 8 OF 8 CAPLUS COPYRIGHT 2002 ACS

AN 1997:375290 CAPLUS

DN 127:86110

TI Method of reducing TNF.alpha. levels with amino-substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo- and 1,3-dioxoisoindolines

IN Muller, George W.; Stirling, David I.; Chen, Roger S. -c

PA Celgene Corp., USA

SO U.S., 7 pp.
CODEN: USXXAM

DT Patent

LA English

FAN.CNT 7

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 5635517	A	19970603	US 1996-690258	19960724
US 5635517	B1	19990629		
CA 2261762	AA	19980129	CA 1997-2261762	19970724
WO 9803502	A1	19980129	WO 1997-US13375	19970724

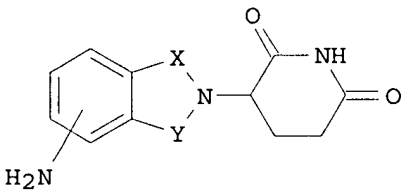
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

	AU 9738998	A1	19980210	AU 1997-38998	19970724
	AU 715779	B2	20000210		
	EP 925294	A1	19990630	EP 1997-936295	19970724
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	CN 1239959	A	19991229	CN 1997-180299	19970724
	JP 2001503384	T2	20010313	JP 1998-507259	19970724
	RU 2177944	C2	20020110	RU 1999-103124	19970724
	FI 9900101	A	19990319	FI 1999-101	19990119
	US 6281230	B1	20010828	US 2000-543809	20000406
	US 6476052	B1	20021105	US 2000-633908	20000807
	US 6316471	B1	20011113	US 2000-634061	20001017
	US 6335349	B1	20020101	US 2000-716528	20001120
	US 2002045643	A1	20020418	US 2001-781179	20010212
PRAI	WO 1994-US7411	A	19940701		
	US 1996-690258	A	19960724		
	US 1996-701499	A1	19960724		
	US 1996-701494	A	19960822		
	US 1997-48278P	P	19970530		
	WO 1997-US13375	W	19970724		
	US 1999-230389	B3	19990507		
	US 2000-543804	A3	20000406		
	US 2000-543809	A1	20000406		

OS MARPAT 127:86110

GI



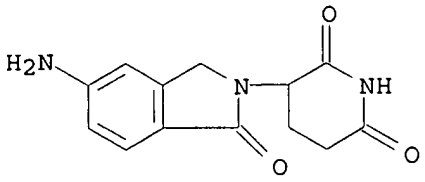
I

AB 1-Oxo- and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)isoindolines (I; 1 of X, Y = C:O; other of X, Y = C:O, CH2) substituted with amino in the benzo ring are prepd. which reduce the levels of TNF.alpha. in a mammal. I are therefore useful in treatment of inflammatory, infectious, immunol., or malignant diseases. Thus, 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline (II) was prepd. by catalytic hydrogenation of the corresponding 5-nitro compd. (prepd. from 4-nitrophthalic anhydride and .alpha.-aminoglutarimide-HCl) over Pd/C. Tablets each contg. 50 mg II were prepd. from a mixt. of II 50.0, lactose 50.7, wheat starch 7.5, PEG-6000 5.0, talc 5.0, Mg stearate 1.8 g, and sufficient water for granulation.

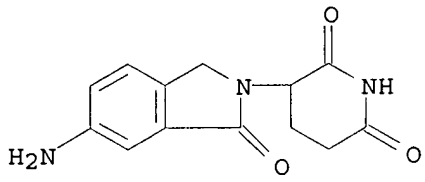
IT **191732-70-4P 191732-74-8P 191732-75-9P**
191732-76-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of reducing TNF.alpha. levels with amino-substituted dioxopiperidinyloxo- and dioxoisoindolines)

RN 191732-70-4 CAPLUS

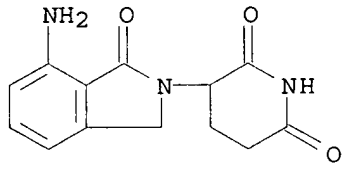
CN 2,6-Piperidinedione, 3-(5-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



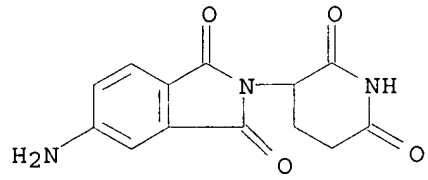
RN 191732-74-8 CAPLUS
CN 2,6-Piperidinedione, 3-(6-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



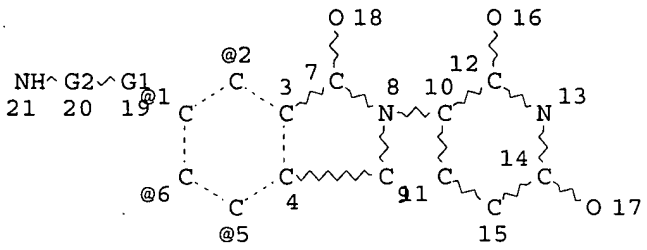
RN 191732-75-9 CAPLUS
CN 2,6-Piperidinedione, 3-(7-amino-1,3-dihydro-1-oxo-2H-isoindol-2-yl)- (9CI) (CA INDEX NAME)



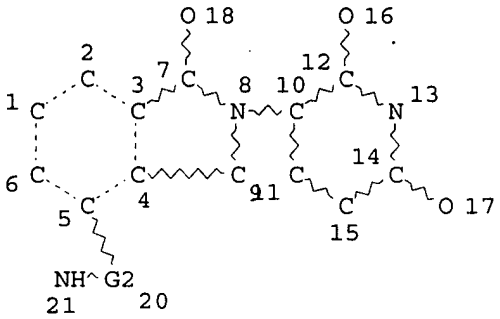
RN 191732-76-0 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 5-amino-2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)



```
=> d l1
L1 HAS NO ANSWERS
L1                STR
```




```
VAR G1=2/1/6/5
REP G2=(0-1) CH
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RSPEC   1  10
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE


=> s l1 ful
FULL SEARCH INITIATED 17:18:24 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED -   1054 TO ITERATE

100.0% PROCESSED    1054 ITERATIONS                          175 ANSWERS
SEARCH TIME: 00.00.01

L3          175 SEA SSS FUL L1
```




```
REP G2=(0-1) CH
ENTER (DIS), GRA, NOD, BON OR ?:end
L4   STRUCTURE CREATED

=> search l4
ENTER TYPE OF SEARCH (SSS), CSS, FAMILY, OR EXACT:sss
ENTER SCOPE OF SEARCH (SAMPLE), FULL, RANGE, OR SUBSET:subset
ENTER SUBSET L# OR (END):l3
ENTER SUBSET SEARCH SCOPE - SAMPLE, FULL, RANGE, OR (END):ful
FULL SUBSET SEARCH INITIATED 17:20:35 FILE 'REGISTRY'
FULL SUBSET SCREEN SEARCH COMPLETED -    167 TO ITERATE

100.0% PROCESSED     167 ITERATIONS                          166 ANSWERS
SEARCH TIME: 00.00.02
```

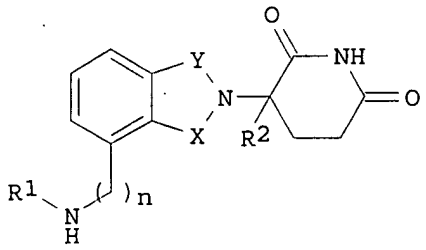
```
     (FILE 'HOME' ENTERED AT 17:14:40 ON 06 DEC 2002)

     FILE 'REGISTRY' ENTERED AT 17:14:53 ON 06 DEC 2002
L1                STRUC
L2             10 S L1
L3            175 S L1 FUL
L4                STRUC
L5            166 SEARCH L4 SSS  SUB=L3 FUL

     FILE 'CAPLUS' ENTERED AT 17:20:41 ON 06 DEC 2002
L6             17 S L5

     FILE 'REGISTRY' ENTERED AT 17:21:25 ON 06 DEC 2002
L7              9 S L3 NOT L5

     FILE 'CAPLUS' ENTERED AT 17:22:03 ON 06 DEC 2002
L8              8 S L7

     FILE 'REGISTRY' ENTERED AT 17:24:22 ON 06 DEC 2002
L9              4 S L5 AND (3R OR 3S)

     FILE 'CAPLUS' ENTERED AT 17:27:36 ON 06 DEC 2002
L10             6 S L9

     FILE 'STNGUIDE' ENTERED AT 17:28:46 ON 06 DEC 2002

     FILE 'REGISTRY' ENTERED AT 17:29:37 ON 06 DEC 2002

=> s l3 and furan?
        757911 FURAN?
L11         11 L3 AND FURAN?

=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       4.38     317.46

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                         ENTRY    SESSION
CA SUBSCRIBER PRICE                                       0.00     -19.21

FILE 'CAPLUS' ENTERED AT 17:29:59 ON 06 DEC 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2002 AMERICAN CHEMICAL SOCIETY (ACS)
```


FILE COVERS 1907 - 6 Dec 2002 VOL 137 ISS 24
FILE LAST UPDATED: 5 Dec 2002 (20021205/ED)

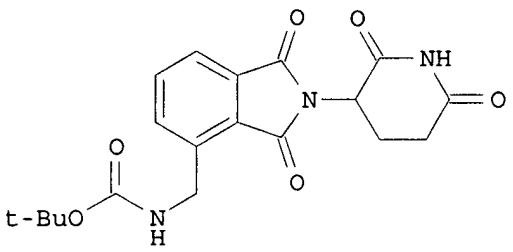
This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

```
=> s l11
L12           1 L11

=> d bib abs

L12  ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2002 ACS
AN   2002:575064  CAPLUS
DN   137:125091
TI   Preparation of 2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-diones, related
     compounds, and compositions thereof as TNF-.alpha. inhibitors for
     treatment of cancer, inflammatory disorders, heart disease, and related
     disorders
IN   Robarge, Michael J.; Chen, Roger Shen-Chu; Muller, George W.; Man, Hon-Wah
PA   Celgene Corporation, USA
SO   PCT Int. Appl., 224 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
     ---------------    ----  --------       ---------------   --------
PI   WO 2002059106      A1    20020801       WO 2001-US50401   20011221
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,
             UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
             CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI US 2000-258372P    P     20001227
     US 2001-972487     A     20011005
OS   MARPAT 137:125091
GI
```



I



II

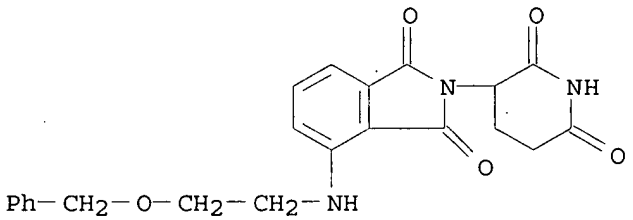
AB Title isoindole-imides I [wherein one of X and Y is CO and the other is CH2 or CO; R1 = H, (cyclo)alkyl, alkenyl, alkynyl, benzyl, aryl, alkylheterocycloalkyl, alkylheteroaryl, COR3, CSR3, CO2R4, alkyl-(NR6)2, alkyl-OR5, alkyl-CO2R5, CONHR3, CSNHR3, CON(R3)2, CSN(R3)2, or alkyl-OCOR5; R2 = H, benzyl, alkyl, alkenyl, or alkynyl; R3 = independently (cyclo)alkyl, alkenyl, alkynyl, benzyl, aryl, alkylheterocycloalkyl, alkylheteroaryl, alkyl-N(R6)2, alkyl-OR5, alkyl-CO2R5, alkyl-OCOR5, or CO2R5; R4 = alkyl, alkenyl, alkynyl, alkyl-OR5, benzyl, aryl, alkylheterocycloalkyl, or alkylheteroaryl; R5 = alkyl, alkenyl, alkynyl, benzyl, aryl, or heteroaryl; R6 = independently H, alkyl, alkenyl, alkynyl, benzyl, (hetero)aryl, or alkyl-CO2R5; or R6 groups may join to form a heterocycloalkyl group; n = 0-1; with the proviso that when n = 0, R1 .noteq. H; or pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, or mixts. of stereoisomers thereof] were prepd. for reducing the level of cytokines and their precursors in mammals. In particular, the invention pertains to isoindole-imide compds. that are potent inhibitors of the prodn. of TNF-.alpha. (no data). For example, Me 2-(methoxycarbonyl)-3-nitrobenzoate was hydrogenated with 10% Pd/C (87%). The amine was converted to the nitrile by diazonium salt formation effected by treatment with NaNO3 followed by cyanide formation using classic Sandmeyer procedure (65%). The nitrile was reduced with 10% Pd/C in MeOH and aq. HCl under hydrogen to afford Me 3-aminomethyl-2-(methoxycarbonyl)benzoate.bul.HCl (90%), which was treated with TEA and then reacted with di-t-Bu dicarbonate to give the carbamate (93%). Cyclization with 3-aminoglutarimide.bul.HCl using diisopropylethylamine in DMF produced II (82%). The 2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-diones and pharmaceutical compns. comprising them are useful for treating or preventing diseases or disorders in mammals, e.g. cancers, such as solid tumors and blood-born tumors; heart disease, such as congestive heart failure; osteoporosis; and genetic, inflammatory, allergic, and autoimmune diseases (no data).

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> s l3 and methoxy
3006858 METHOXY
L13 10 L3 AND METHOXY

=> d scan

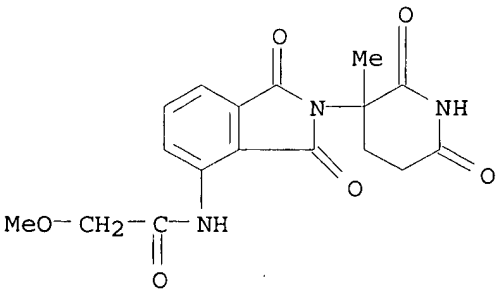
L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-4-[[2-(phenylmethoxy)ethyl]amino]- (9CI)**
MF C22 H21 N3 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

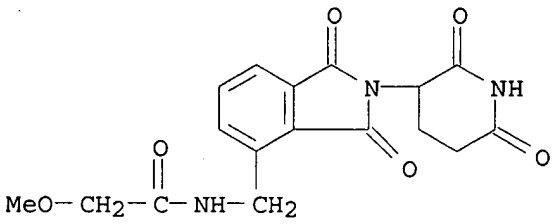
HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):9

L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **Acetamide, N-[2,3-dihydro-2-(3-methyl-2,6-dioxo-3-piperidinyl)-1,3-dioxo-1H-isoindol-4-yl]-2-methoxy- (9CI)**
MF C17 H17 N3 O6



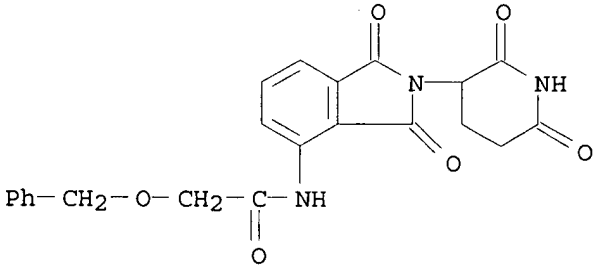
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **Acetamide, N-[[2-(2,6-dioxo-3-piperidinyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]methyl]-2-methoxy- (9CI)**
MF C17 H17 N3 O6



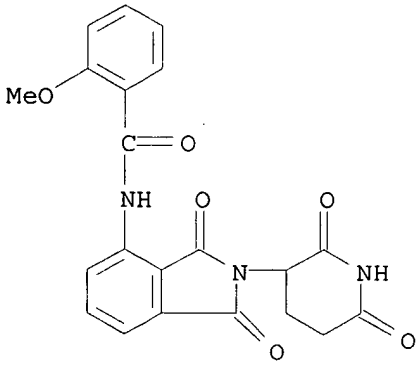
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **Acetamide, N-[2-(2,6-dioxo-3-piperidinyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-2-(phenylmethoxy)- (9CI)**
MF C22 H19 N3 O6



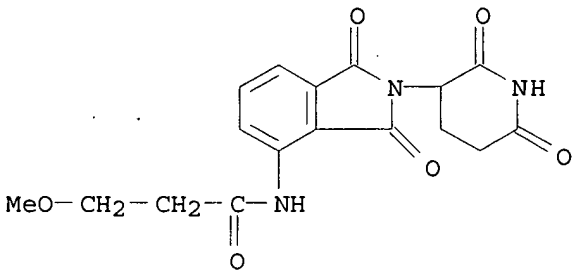
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **Benzamide, N-[2-(2,6-dioxo-3-piperidinyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-2-methoxy- (9CI)**
MF C21 H17 N3 O6



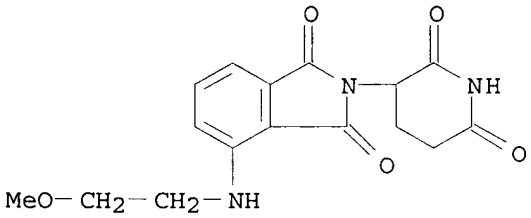
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **Propanamide, N-[2-(2,6-dioxo-3-piperidinyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-3-methoxy- (9CI)**
MF C17 H17 N3 O6



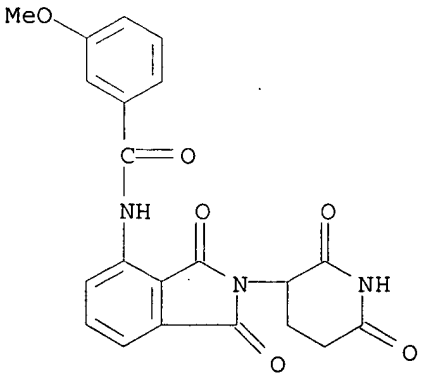
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

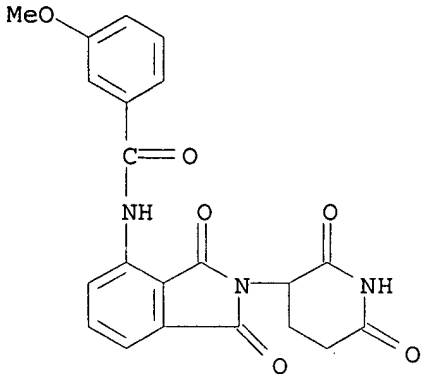
L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **1H-Isoindole-1,3(2H)-dione, 2-(2,6-dioxo-3-piperidinyl)-4-[(2-methoxyethyl)amino]- (9CI)**
MF C16 H17 N3 O5



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

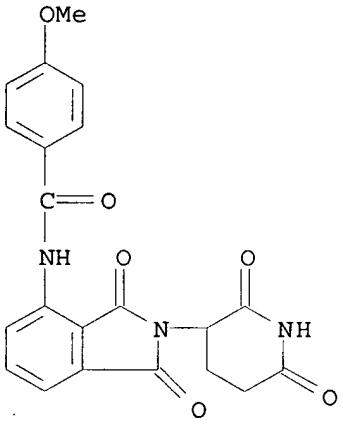
L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **Benzamide, N-[2-(2,6-dioxo-3-piperidinyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-3-methoxy- (9CI)**
MF C21 H17 N3 O6





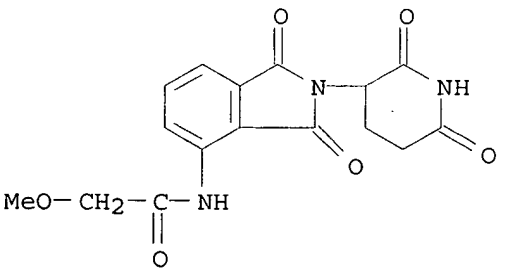
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **Benzamide, N-[2-(2,6-dioxo-3-piperidinyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-4-methoxy- (9CI)**
MF C21 H17 N3 O6



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L13 10 ANSWERS REGISTRY COPYRIGHT 2002 ACS
IN **Acetamide, N-[2-(2,6-dioxo-3-piperidinyl)-2,3-dihydro-1,3-dioxo-1H-isoindol-4-yl]-2-methoxy- (9CI)**
MF C16 H15 N3 O6



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

ALL ANSWERS HAVE BEEN SCANNED

=> fil caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	5.52	325.67

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-19.83

FILE 'CAPLUS' ENTERED AT 17:33:08 ON 06 DEC 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 6 Dec 2002 VOL 137 ISS 24
FILE LAST UPDATED: 5 Dec 2002 (20021205/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

CAS roles have been modified effective December 16, 2001. Please check your SDI profiles to see if they need to be revised. For information on CAS roles, enter HELP ROLES at an arrow prompt or use the CAS Roles thesaurus (/RL field) in this file.

=> s l13
L14 1 L13

=> d bib

L14 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2002 ACS
AN 2002:575064 CAPLUS
DN 137:125091
TI Preparation of 2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-diones, related compounds, and compositions thereof as TNF-.alpha. inhibitors for treatment of cancer, inflammatory disorders, heart disease, and related disorders
IN Robarge, Michael J.; Chen, Roger Shen-Chu; Muller, George W.; Man, Hon-Wah
PA Celgene Corporation, USA
SO PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	WO 2002059106	A1	20020801	WO 2001-US50401	20011221

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 2000-258372P	P	20001227
	US 2001-972487	A	20011005

OS MARPAT 137:125091

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s l5 and (3R or 3S)
        162073 3R
        155519 3S
L9           4 L5 AND (3R OR 3S)
```

=> s l9
L10 6 L9

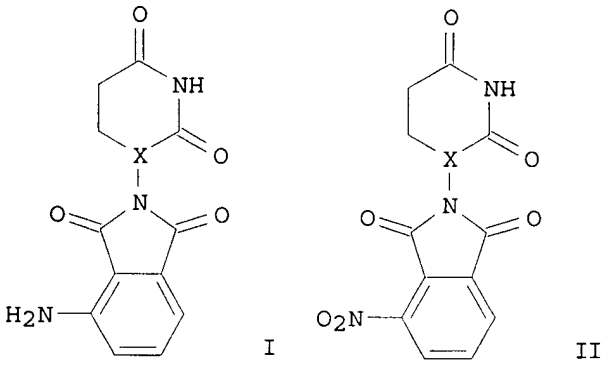
=> d bib abs hitstr 1-6

L10 ANSWER 1 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 2002:637473 CAPLUS
DN 137:185418
TI Enantioselective preparation of 3-aminothalidomides for the treatment of diseases that are mediated by abnormal mitosis and/or angiogenesis
IN Treston, Anthony; Shah, Jamshed H.; D'Amato, Robert J.; Hunsucker, Kimberly A.; Rougas, John; Conner, Barry P.; Pribluda, Victor; Swartz, Glenn M.
PA The Children's Medical Center Corporation, USA
SO PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002064083	A2	20020822	WO 2001-US45229	20011130

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-250219P P 20001130
GI



I II

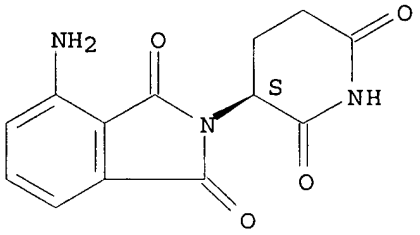
AB Title compds. I [X = CH, (R)-enantiomer, (S)-enantiomer, (R,S) racemate] and their formulations were prepd. For example, condensation of (3S)-aminoglutarimide, e.g., prepd. from N-CBZ-L-glutamine in 2 steps, and 3-nitrophthalic anhydride provided nitrothalidomide II [X = CH, (S)-enantiomer], followed by nitro redn. afforded claimed aminothalidomide I [X = CH, (S)-enantiomer]. In vivo expts. in lung and plasma cell tumor metastatic tumor systems comparing the antitumor activity of the three enantiomeric prepns. of I, demonstrated the S-enantiomer to be the most active enantiomer in each tumor model. Compds. I are useful for the

treatment of angiogenesis-assocd. diseases, e.g., cancer and macular degeneration.

IT **202271-89-4P 202271-90-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; enantioselective prepn. of 3-aminothalidomides as mitotic and/or angiogenic inhibitors)

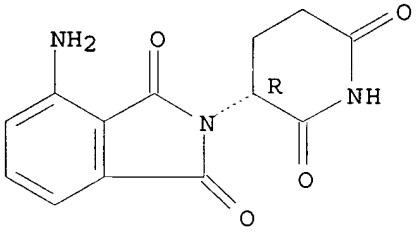
RN 202271-89-4 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3S)-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 202271-90-7 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L10 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 2002:323075 CAPLUS
DN 137:241801
TI S-3-amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice
AU Lentzsch, Suzanne; Rogers, Michael S.; LeBlanc, Richard; Birsner, Amy E.; Shah, Jamshed H.; Treston, Anthony M.; Anderson, Kenneth C.; D'Amato, Robert J.
CS Jerome Lipper Multiple Myeloma Center, Department of Adult Oncology, Dana-Farber Cancer Institute and Department of Medicine, Harvard Medical School, Boston, MA, 02115, USA
SO Cancer Research (2002), 62(8), 2300-2305
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Thalidomide has recently been shown to be useful in the treatment of multiple myeloma and may also be useful in the treatment of other hematol. malignancies. We have identified a new deriv. of thalidomide, S-3-[3-amino-phthalimido]-glutarimide (S-3APG) with dual activity against B-cell neoplasias. S-3APG was able to directly inhibit the proliferation of myeloma and Burkitt's lymphoma cell lines in vitro without showing

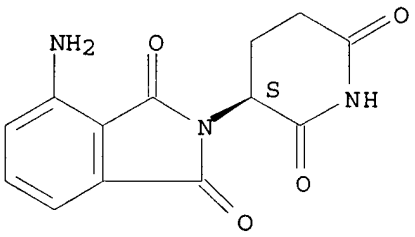
toxicity to normal bone marrow stromal cells or hematopoietic progenitor cells. In vivo, S-3APG treatment of drug resistant myeloma cell tumors in mice was able to produce complete and sustained regressions without any obsd. toxicity. Addnl., S-3APG induced complete regressions of Burkitt's lymphoma cell tumors. Furthermore, S-3APG inhibited angiogenesis more potently than thalidomide in the murine corneal micropocket model. We conclude that S-3APG is a powerful anti-myeloma and anti-B-cell-lymphoma agent that has both anti-proliferative and antiangiogenic effects.

IT **202271-89-4**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(S-3APG inhibits angiogenesis and growth of B-cell neoplasias in mice)

RN 202271-89-4 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3S)-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2002 ACS

AN 2002:211227 CAPLUS

DN 137:241664

TI Thalidomide and its analogues as cyclooxygenase inhibitors

AU Noguchi, Tomomi; Shimazawa, Rumiko; Nagasawa, Kazuo; Hashimoto, Yuichi

CS Institute of Molecular & Cellular Biosciences, The University of Tokyo, Bunkyo-ku, Tokyo, 113-0032, Japan

SO Bioorganic & Medicinal Chemistry Letters (2002), 12(7), 1043-1046
CODEN: BMCLE8; ISSN: 0960-894X

PB Elsevier Science Ltd.

DT Journal

LA English

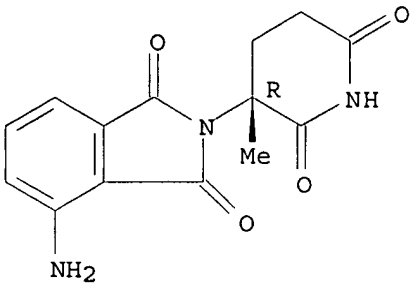
AB Thalidomide showed cyclooxygenase (COX)-1/2 inhibitory activity with a potency comparable to that of aspirin. Structural development studies of thalidomide resulted in potent COX-1/2 inhibitors, and COX-1-selective and COX-2-selective inhibitors.

IT **212394-04-2**
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thalidomide and analogs as cyclooxygenase inhibitors)

RN 212394-04-2 CAPLUS

CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

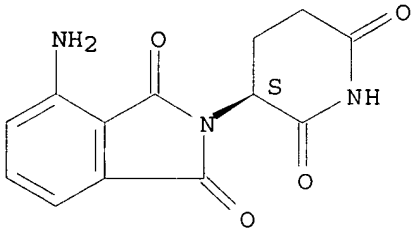
Absolute stereochemistry. Rotation (-).



RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

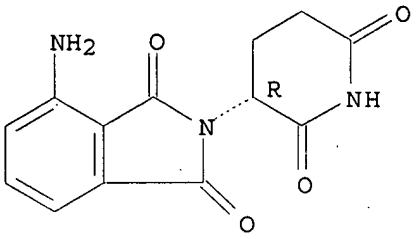
L10 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 1999:386135 CAPLUS
DN 131:129881
TI Amino-substituted thalidomide analogs: potent inhibitors of TNF-.alpha. production
AU Muller, George W.; Chen, Roger; Huang, Shaei-Yun; Corral, Laura G.; Wong, Lu Min; Patterson, Rebecca T.; Chen, Yuxi; Kaplan, Gilla; Stirling, David I.
CS Celgene Corporation, Warren, NJ, 07059, USA
SO Bioorganic & Medicinal Chemistry Letters (1999), 9(11), 1625-1630
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB Thalidomide is a known inhibitor of TNF-.alpha. release in LPS stimulated human PBMC. Herein we describe the TNF-.alpha. inhibitory activity of amino substituted analogs of thalidomide and its isoindolin-1-one analog, EM-12. The 4-amino substituted analogs were found to be potent inhibitors of TNF-.alpha. release in LPS stimulated human PBMC.
IT **202271-89-4P 202271-90-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(amino derivs. of thalidomide and EM-12 as inhibitors of TNF-.alpha. prodn.)
RN 202271-89-4 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3S)-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 202271-90-7 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

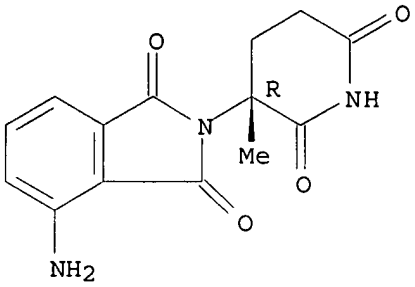
Absolute stereochemistry. Rotation (+).



RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

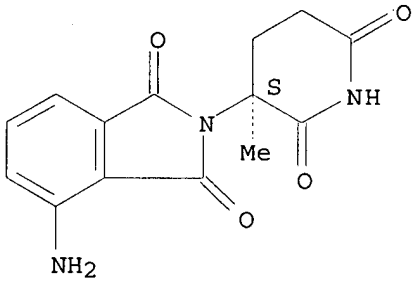
L10 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 1998:486299 CAPLUS
DN 129:216494
TI Tumor necrosis factor-alpha production enhancing activity of substituted 3'-methylthalidomide: influence of substituents at the phthaloyl moiety on the activity and stereoselectivity
AU Miyachi, Hiroyuki; Kolso, Yukiko; Shirai, Ryuichi; Niwayama, Satomi; Liu, Jun O.; Hashimoto, Yuichi
CS Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, 113-0032, Japan
SO Chemical & Pharmaceutical Bulletin (1998), 46(7), 1165-1168
CODEN: CPBTAL; ISSN: 0009-2363
PB Pharmaceutical Society of Japan
DT Journal
LA English
OS CASREACT 129:216494
AB The synthesis and tumor necrosis factor (TNF)-.alpha. prodn. enhancing activity of substituted 3'-methyl-thalidomides on human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate (TPA) was described. Though the introduction of an electron-donating amino group at the phthaloyl moiety of .alpha.-methylthalidomides enhanced the activity, substituted .alpha.-methylthalidomides showed decreased stereoselectivity as compared to that of non-substituted .alpha.-methylthalidomide. The data indicates that the TNF-.alpha. prodn. enhancing activity of thalidomide derivs. depends on both the electronic-state of substituents at the fused benzene ring and the stereochem. of the glutarimide moiety. (S)-4-amino-3'-methylthalidomide induced a 695% increase in the amt. of tumor necrosis factor-alpha prodn. at 0.3.mu.m by the human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate.
IT **212394-04-2P 212394-05-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tumor necrosis factor-alpha prodn. enhancing activity of substituted 3'-methylthalidomides)
RN 212394-04-2 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 212394-05-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3S)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L10 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 1998:87727 CAPLUS
DN 128:140615
TI Substituted 2-(2,6-dioxo-3-piperidinyl)phthalimides and -1-oxoisoindolines and method of reducing TNF-.alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu
PA Celgene Corp., USA; Muller, George W.; Stirling, David I.; Chen, Roger Shen-Chu
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

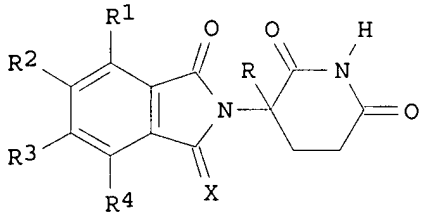
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9803502	A1	19980129	WO 1997-US13375	19970724
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5635517	A	19970603	US 1996-690258	19960724
US 5635517	B1	19990629		
US 5798368	A	19980825	US 1996-701494	19960822
AU 9738998	A1	19980210	AU 1997-38998	19970724
AU 715779	B2	20000210		
EP 925294	A1	19990630	EP 1997-936295	19970724

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

	JP 2001503384	T2	20010313	JP 1998-507259	19970724
	RU 2177944	C2	20020110	RU 1999-103124	19970724
	FI 9900101	A	19990319	FI 1999-101	19990119
	US 6281230	B1	20010828	US 2000-543809	20000406
	US 6476052	B1	20021105	US 2000-633908	20000807
	US 6316471	B1	20011113	US 2000-634061	20001017
	US 6335349	B1	20020101	US 2000-716528	20001120
	US 2002045643	A1	20020418	US 2001-781179	20010212
	US 2002183360	A1	20021205	US 2002-119486	20020410
PRAI	US 1996-690258	A	19960724		
	US 1996-701494	A	19960822		
	WO 1994-US7411	A	19940701		
	US 1996-701499	A1	19960724		
	US 1997-48278P	P	19970530		
	WO 1997-US13375	W	19970724		
	US 1999-230389	B3	19990507		
	US 2000-543804	A3	20000406		
	US 2000-543809	A1	20000406		
	US 2000-633908	A1	20000807		

OS MARPAT 128:140615

GI



I

AB Title compds. I (X = O, H2; R = H, alkyl, benzyl, halo; R1, R2, R3, R4 = H, alkyl, alkoxy, halo, amino) were prepd. for TNF-.alpha. redn. in mammals. Thus, I (X = O, R = R1 = R3 = R4 = H, R2 = NO2), prepd. from 4-nitrophthalic anhydride and .alpha.-aminoglutarimide hydrochloride, was hydrogenated over 10% Pd/C in 1,4-dioxane at 50 psi for 6.5 h to give 69% I (X = O, R = R1 = R3 = R4 = H, R2 = NH2). Several examples of formulations were given.

IT **202271-89-4P 202271-90-7P**

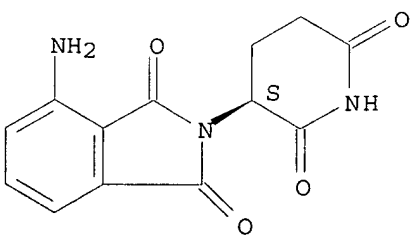
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(2-(2,6-dioxo-3-piperidinyl)phthalimides and -1-oxoisoindolines for reducing TNF-.alpha. levels)

RN 202271-89-4 CAPLUS

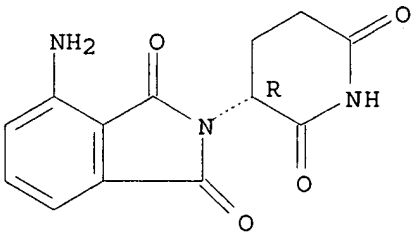
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3S)-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 202271-90-7 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-2,6-dioxo-3-piperidinyl]-
(9CI) (CA INDEX NAME)

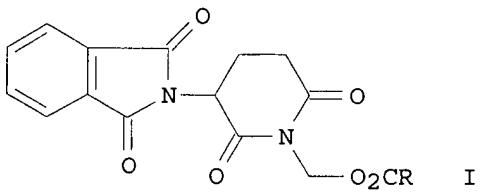
Absolute stereochemistry. Rotation (+).



AN 1997:684400 CAPLUS
DN 127:331403
TI Acylated N-hydroxymethylthalidomide prodrugs with immunomodulator action
IN Schneider, Johannes; Winter, Werner; Wnendt, Stephan; Zwingenberger, Kai; Eger, Kurt; Akermann, Michaela
PA Grunenthal G.m.b.H., Germany; Schneider, Johannes; Winter, Werner; Wnendt, Stephan; Zwingenberger, Kai; Eger, Kurt; Akermann, Michaela
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9737988	A1	19971016	WO 1997-EP1475	19970322
	W: AU, CA, CN, HU, JP, LT, LV, MX, SI, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	DE 19613976	C1	19971120	DE 1996-19613976	19960409
	CA 2251060	AA	19971016	CA 1997-2251060	19970322
	AU 9725052	A1	19971029	AU 1997-25052	19970322
	AU 707144	B2	19990701		
	EP 892794	A1	19990127	EP 1997-916380	19970322
	EP 892794	B1	20020206		
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
	CN 1215397	A	19990428	CN 1997-193682	19970322
	JP 2000508298	T2	20000704	JP 1997-535786	19970322
	AT 212989	E	20020215	AT 1997-916380	19970322
	ES 2171923	T3	20020916	ES 1997-916380	19970322
	US 6417197	B1	20020709	US 1998-155896	19981214
PRAI	DE 1996-19613976	A	19960409		
	WO 1997-EP1475	W	19970322		

OS MARPAT 127:331403
GI



I

AB Thalidomide prodrugs I [R = CHR1NHR2, (CH2)nCO2H; R1 = H, alkyl; R2 = H, alkyl, COCH2NHR3, amine protective group; R3 = H, amino protective group; n = 2-4] and their salts were prepd. Thus, N-hydroxymethylthalidomide was acylated with N-tert-butoxycarbonylglycine and deblocked to give I.HCl [R = CH2NH2] which gave 68% inhibition of serum IL-2 increase at 400 mg/kg.

AN 1997:803809 CAPLUS
DN 128:53204
TI Prodrugs of thalidomide and methods for using same as modulators of T-cell function
IN Smith, Robert E.
PA Prototek, Inc., USA; Smith, Robert E.
SO PCT Int. Appl., 20 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9745117	A1	19971204	WO 1997-US9421	19970529
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9732249	A1	19980105	AU 1997-32249	19970529
	EP 914123	A1	19990512	EP 1997-927902	19970529
	R: BE, CH, DE, DK, FR, GB, IT, LI, NL				
PRAI	US 1996-18558P	P	19960529		
	WO 1997-US9421	W	19970529		

AB The present invention relates to a new, safe and effective form of **thalidomide** (N-phthalimido glutarimide) and methods of using the same. More specifically, the invention relates to **prodrugs** of **thalidomide** and **prodrugs** of certain analogs of **thalidomide**, which comprise a **thalidomide** or analog component having bound thereto the dipeptide sequence X-pro, wherein X is one of a wide variety of **amino** acids and pro represents the imino acid proline.

=> s thalidomide(l)(paclitzxel or cisplatin or tamoxifen or docetaxel or epirubicin or leuprolide or bicalutamide or goserelin or gemcitabine or sargramostim)

```
          1484 THALIDOMIDE
             0 PACLITZXEL
         13312 CISPLATIN
          6770 TAMOXIFEN
          1303 DOCETAXEL
          1309 EPIRUBICIN
           649 LEUPROLIDE
           209 BICALUTAMIDE
           338 GOSERELIN
          1264 GEMCITABINE
            48 SARGRAMOSTIM
L1          12 THALIDOMIDE(L)(PACLITZXEL OR CISPLATIN OR TAMOXIFEN OR DOCETAXEL
               OR EPIRUBICIN OR LEUPROLIDE OR BICALUTAMIDE OR GOSERELIN OR
               GEMCITABINE OR SARGRAMOSTIM)
```

=> d bib abs 1-12

L1 ANSWER 1 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2002:851663 CAPLUS
DN 137:345733
TI A high rate of venous thromboembolism in a multi-institutional phase II trial of weekly intravenous **gemcitabine** with continuous infusion fluorouracil and daily **thalidomide** in patients with metastatic renal cell carcinoma
AU Desai, Apurva A.; Vogelzang, Nicholas J.; Rini, Brian I.; Ansari, Rafat; Krauss, Stuart; Stadler, Walter M.
CS Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL, USA
SO Cancer (New York, NY, United States) (2002), 95(8), 1629-1636
CODEN: CANCAR; ISSN: 0008-543X
PB John Wiley & Sons, Inc.
DT Journal
LA English
AB The objective of this study was to det. the clin. response rate of the combination of weekly i.v. (IV) **gemcitabine** with continuous infusion fluorouracil (5-FU) and daily oral **thalidomide** in patients with metastatic renal cell carcinoma (RCC). Between June, 2000 and Jan., 2001, 21 patients with metastatic RCC were enrolled onto this multi-institutional Phase II study of **gemcitabine** at 600 mg/m2 per day on Days 1, 8, and 15; 5-FU at 150 mg/m2 per day by continuous IV infusion through a permanent catheter on Days 1-21; and oral **thalidomide** on Days 1-28 starting at a dose of 200 mg daily. After the first 2 wk of therapy, the **thalidomide** dose was escalated by 100 mg per day every week to a max. dose of 400 mg per day unless it was precluded by toxicity. Treatment cycles were repeated every 28 days. A high rate of venous thromboembolism (VTE) was obsd. Five patients developed deep vein thrombosis (DVT), three patients developed pulmonary embolization (PE), and one patient suffered a fatal cardiac arrest preceded by hemoptysis, for an overall VTE rate of 43%. Of the 18 assessable patients, there were no complete responses and 2 partial responses (objective response rate, 10%; 95% confidence interval, 1-30%). The addn. of **thalidomide** to **gemcitabine** and 5-FU did not improve the objective response rate previously obsd. with **gemcitabine** and 5-FU alone and added significant vascular toxicity. The authors recommend against further development or use of this three-drug regimen.
RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 2 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2002:694230 CAPLUS
DN 137:226327
TI Thalidomide paradoxical effect on concomitant multiple myeloma and myelodysplasia
AU Badros, Ashraf; Morris, Christopher; Zangari, Maurizio; Barlogie, Bart; Tricot, Guido
CS Myeloma and Transplantation Research Center, University of Arkansas for Medical Sciences, Little Rock, AR, USA
SO Leukemia & Lymphoma (2002), 43(6), 1267-1271
CODEN: LELYEA; ISSN: 1042-8194
PB Taylor & Francis Ltd.
DT Journal
LA English
AB We present five cases of concomitant relapsed multiple myeloma and therapy related myelodysplasia (t-MDS). After treatment with thalidomide marked anti-myeloma activity was obsd., but it was assocd. with rapid progression of the MDS clone to acute myeloid leukemia (AML). This paradoxical effect of thalidomide is concerning because there is increasing use of thalidomide in relapsed, heavily treated multiple mycloma patients who already have a higher propensity to develop MDS. The leukemic transformation in our cases most probably reflects the natural progression of MDS, though it clearly demonstrates that thalidomide is ineffective in controlling blast proliferation in t-MDS. More concerning, however, is the possibility that thalidomide, while suppressing the myeloma clone, eliminates inhibitory signals and subsequently stimulates the proliferation of the leukemic clone. The use of thalidomide should be carefully assessed in relapsed multiple myeloma patients with clin. and cytogenetic evidence of t-MDS.
RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 3 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2002:677730 CAPLUS
TI Antitumorigenic evaluation of **thalidomide** alone and in combination with **cisplatin** in DBA2/J mice
AU Ruddy, Jean Marie B.; Majumdar, Shyamal K.
CS Department of Biology, Lafayette College, Easton, PA, 18042, USA
SO Journal of Biomedicine & Biotechnology (2002), 2(1), 7-13
CODEN: JBBOAJ; ISSN: 1110-7243
PB Hindawi Publishing Corporation
DT Journal
LA English
AB **Thalidomide**'s reported ability to inhibit angiogenesis has led to clin. trials detg. its effectiveness in combating various types of cancer. This study explored **thalidomide**'s antitumorigenic potential when administered alone and in combination with **cisplatin** to DBA2/J mice whose tumors were induced by murine erythroleukemic cells. **Thalidomide** treatment alone produced no significant inhibitory effect on tumor development and metastasis. Mice that received both drugs had significantly lower incidences of both primary and secondary tumors as compared to the untreated control group. **Cisplatin**, administered alone or in combination with **thalidomide**, led to a significant delay in tumor formation and a longer life span than was recorded in untreated mice. However, the combination treatment results were not significantly different from those of **cisplatin** treatment used as a single agent. In in vitro cell multiplication studies using murine erythroleukemic and murine endothelial cells, **thalidomide** failed to inhibit cell proliferation. However, **cisplatin** treatment with or without **thalidomide**, significantly inhibited the multiplication of both cell lines in a dose dependent manner. **Thalidomide** does not appear to be a beneficial adjuvant to **cisplatin** treatment.

RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2002:659562 CAPLUS
DN 137:210282
TI Pharmacokinetic considerations of oral chemotherapy in elderly patients with cancer
AU Skirvin, J. Andrew; Lichtman, Stuart M.
CS College of Pharmacy and Allied Health Professions, St Johns University, Jamaica, NY, USA
SO Drugs & Aging (2002), 19(1), 25-42
CODEN: DRAGE6; ISSN: 1170-229X
PB Adis International Ltd.
DT Journal; General Review
LA English
AB A review. Persons over the age of 65 yr are the fastest growing segment of the US population. In the next 30 yr they will comprise over 20% of the population. Fifty per cent of all cancers occur in this age group and therefore there will be an expected rise in the total cancer burden. There has been an increasing trend over the past 20 yr toward the use of oral chemotherapy. This change has been encouraged by the need to decrease the costs of chemotherapy administration, patient preferences and quality of life issues. Factors that must be considered with oral chemotherapy administration include limitations of saturability of absorption, patient compliance and pharmacokinetic/pharmacodynamic changes which occur in elderly patients. Interpatient variability and drug metab., particularly age-related changes in drug metab. are being studied. The cytochrome P 450 system has been intensively studied because of its importance with regard to chemotherapeutic drugs. This article reviews these issues and provides details regarding specific drugs including temozolomide, **thalidomide**, topotecan, the fluoropyrimidines, etoposide, hydroxycarbamide (hydroxyurea), **tamoxifen**, and alkylating drugs. Complementary and alternative therapies are also discussed.
RE.CNT 138 THERE ARE 138 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 5 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2002:629151 CAPLUS
DN 137:195160
TI Thrombogenic activity of doxorubicin in myeloma patients receiving thalidomide: implications for therapy
AU Zangari, Maurizio; Siegel, Eric; Barlogie, Bart; Anaissie, Elias; Saghafifar, Fariba; Fassas, Athanasios; Morris, Christopher; Fink, Louis; Tricot, Guido
CS Central Arkansas Veterans Healthcare System, Little Rock, AR, USA
SO Blood (2002), 100(4), 1168-1171
CODEN: BLOOAW; ISSN: 0006-4971
PB American Society of Hematology
DT Journal
LA English
AB Ten percent of newly diagnosed myeloma patients treated with any type of chemotherapy develop deep venous thrombosis (DVT). **Thalidomide** has proven activity in refractory multiple myeloma (MM), and although single-agent **thalidomide** has minimal pro-thrombogenic activity, its combination with cytotoxic chemotherapy is assocd. with a significantly increased risk of DVT. We analyzed the incidence of DVT in 232 MM patients who received a combination of chemotherapy and **thalidomide** on 2 protocols that differed only by the inclusion of doxorubicin in one. DT-PACE (dexamethasone/**thalidomide**/**cisplatin**/doxorubicin/cyclophosphanide/etoposide) was offered to patients with preceding std. dose therapy, but no prior

autotransplantation, while DCEP-T (dexamethasone/cyclophosphamide/etoposide/**cisplatin/thalidomide**) was administered for relapse after transplantation. If there were signs or symptoms suggestive of DVT, patients received addnl. investigations, including Doppler ultrasonog., followed by venog. if indicated. Only patients on DT-PACE but not DCEP-T experienced an increased incidence of DVT. A statistical assocn. between the incidence of DVT and combination chemotherapy including doxorubicin (P = .02) was obsd.; this assocn. was confirmed on multivariate anal. MM patients treated with **thalidomide** and doxorubicin have a high risk of developing DVT.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 6 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2002:262835 CAPLUS
DN 137:257308
TI A quantitative angiogenesis model for efficacy testing of chemopreventive agents
AU Sharma, Sheela; Ghoddoussi, Mazyar; Gao, Pu; Kelloff, Gary J.; Steele, Vernon E.; Kopelovich, Levy
CS Cellular and Molecular Toxicology Program, ManTech Environmental Technology, Inc., Research Triangle Park, NC, 27709, USA
SO Anticancer Research (2001), 21(6A), 3829-3837
CODEN: ANTRD4; ISSN: 0250-7005
PB International Institute of Anticancer Research
DT Journal
LA English
AB One of the approaches in chemoprevention to prevent or delay the progression of precancerous lesions, is to apply chemopreventive agents that can potentially block angiogenesis. A quant. in vivo angiogenesis inhibition assay was developed to test the efficacy of twelve chemopreventive agents that represent different chem. classes and multiple biol. activities, using the chick chorioallantoic membrane (CAM) model and an oncogene- transfected angiogenic cell line (6 Ti ras/SV myc # 4). These tumorigenic cells held by a primary agarose pellet, were placed alone or with a secondary pellet incorporating five concns. of the test agent, on an exposed CAM of 7-day-old chick embryo for 72 h in a humidified chamber at 35.degree.. The cell-induced angiogenic blood vessels, including the microvessels radiating from the cell pellet focal area, were scored using a computerized custom image anal. system. The results show that nonsteroidal antiinflammatory drugs (NSAIDS); aspirin, sulindac, sulindac sulfide and sulindac sulfone, were effective inhibitors of cell-induced angiogenesis (23-66%). Aspirin displayed a dose-dependent response with the highest inhibition at 300 .mu.M and an EC50 (the effective molar concn. that inhibits angiogenesis by 50%) of 26.mu.M. Sulindac sulfone was more effective than sulindac with an EC50 of 5 .mu.M vs. 85 .mu.M. However, sulindac sulfide showed an intermediate response with an EC50 of 41 .mu.M. The retinoids; all-trans-retinoic acid (ATRA), 9-cis-retinoic acid (9-cis-RA), and 13-cis-retinoic acid (13-cis-RA) were also highly effective inhibitors of cell-mediated CAM-angiogenesis. 13-Cis-RA with an EC50 of 3.6 nM, has been the most efficacious test agent, > 400-fold more effective than 9-cis-RA (1.5 .mu.M). ATRA exhibited an intermediate response between 9-cis-RA and 13-cis-RA with an EC50 of 0.3 .mu.M, and was 100-fold more efficacious than 9-cis-RA. However, the synthetic retinoid, N-(4-hydroxyphenyl) retinamide (4-HPR), was not an effective inhibitor of CAM angiogenesis. **Thalidomide**, a compd. with multiple biol. activities, exhibited dose-dependent inhibition ranging-from 10-1000 .mu.M with an EC50 of 19 .mu.M. Other agents that exhibited dose-dependent inhibition included Bowman-Birk inhibitor (BBI), EC50: 10 .mu.g/mL, **tamoxifen**, EC50 0.05 .mu.M and difluoromethyl ornithine (DFMO), with an EC50 of 13 .mu.M. These results suggest that tumor-assocd. angiogenesis can be modulated by non-toxic concns. of chemopreventive agents representing multiple biol.

activities and multiple targets.
RE.CNT 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2001:818154 CAPLUS
DN 136:112075
TI Nonsurgical treatment of hepatocellular carcinoma
AU Aguayo, Alvaro; Patt, Yehuda Z.
CS Division of Medicine, Departments of Medical Oncology and Gastrointestinal Medical Oncology, M.D. Anderson Cancer Center, The University of Texas, Houston, TX, 77030, USA
SO Seminars in Oncology (2001), 28(5), 503-513
CODEN: SOLGAV; ISSN: 0093-7754
PB W. B. Saunders Co.
DT Journal; General Review
LA English
AB A review. While surgical resection and tumor ablation are the preferred therapies for hepatocellular carcinoma (HCC), these are available or appropriate in only a minority of patients. This reflects the usual comorbidity of severe underlying liver disease that either precludes surgery or makes the surgical approach extremely dangerous. Nonetheless, regional control of HCC is highly relevant and many regional strategies have been explored, including hepatic intra-arterial chemotherapy, transarterial chemoembolization, lipiodol chemoembolization, radiation therapy, cryosurgery, percutaneous ethanol injection, and radiofrequency ablation. In addn., a variety of systemic chemotherapeutic agents have been tested in HCC, including various combinations of 5-fluorouracil, doxorubicin, **epirubicin**, etoposide, **cisplatin**, and mitoxantrone, as well as interferon, **tamoxifen**, capecitabine, **thalidomide**, and octreotide, Published data regarding these regional and systemic therapies will be discussed in this review.
RE.CNT 119 THERE ARE 119 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2001:803543 CAPLUS
DN 136:112339
TI A randomized phase II trial of **docetaxel** (taxotere) plus **thalidomide** in androgen-independent prostate cancer
AU Figg, William D.; Arlen, Phil; Gulley, James; Fernandez, Patricia; Noone, Marianne; Fedenko, Kathy; Hamilton, Mike; Parker, Catherine; Kruger, Erwin A.; Pluda, James; Dahut, William L.
CS Medicine Branch, Division of Clinical Services, National Cancer Institute, Bethesda, MD, USA
SO Seminars in Oncology (2001), 28(4, Suppl. 15), 62-66
CODEN: SOLGAV; ISSN: 0093-7754
PB W. B. Saunders Co.
DT Journal
LA English
AB New therapeutic alternatives are needed to improve outcomes in patients with androgen-independent prostate cancer (AIPC). For several years, researchers at the National Cancer Institute have been interested in elucidating the importance of angiogenesis in the pathogenesis of prostate cancer and in identifying inhibitors of this process. **Thalidomide** has been shown to inhibit the ability of tumors to recruit new blood vessels. In a recent phase II trial of **thalidomide** in AIPC, 28% of patients achieved a prostate-specific antigen (PSA) decrease of >40%. The taxane **docetaxel** also produces PSA and measurable disease responses when used as monotherapy or as a component of combination chemotherapy for AIPC. Thus, based on the single-agent activity of **thalidomide** and **docetaxel**, we initiated a randomized phase II study of weekly **docetaxel** with or without

thalidomide, 200 mg at bedtime, in patients with chemotherapy-naive metastatic AIPC. **Docetaxel**, 30 mg/m2 i.v., was administered every 7 days for 3 wk, followed by a 1-wk rest period. Both regimens have been well tolerated among the first 59 treated patients, with a near absence of grade 3/4 myelosuppression. Fatigue, hyperglycemia, and pulmonary toxicity were seen in both groups. Thrombotic events have been seen in the combination arm. Thirty-five percent (6 of 17) of the patients receiving **docetaxel** alone and 53% (19 of 36) of those receiving **docetaxel** and **thalidomide** have had a PSA decrease of at least 50%. Combining a cytotoxic agent with an angiogenesis inhibitor is a promising area of investigation for prostate cancer management.

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 9 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2001:695081 CAPLUS
DN 135:366450
TI Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy
AU Zangari, Maurizio; Anaissie, Elias; Barlogie, Bart; Badros, Ashraf; Desikan, Raman; Gopal, A. Viju; Morris, Christopher; Toor, Amir; Siegel, Eric; Fink, Louis; Tricot, Guido
CS Central Arkansas Veterans Healthcare System and the University of Arkansas for Medical Sciences, Little Rock, AR, USA
SO Blood (2001), 98(5), 1614-1615
CODEN: BLOOAW; ISSN: 0006-4971
PB American Society of Hematology
DT Journal
LA English
AB The occurrence of deep-vein thrombosis (DVT) in patients with newly diagnosed multiple myeloma, who were randomly assigned to receive identical induction chemotherapy with or without **thalidomide**, are reported in this study. The 2 study arms were comparable with respect to key myeloma prognostic factors and known risk factors for DVT. One hundred patients received induction chemotherapy including 4 cycles of continuous infusion of combinations of dexamethasone, vincristine, doxorubicin, cyclophosphamide, etoposide, and **cisplatin**, and each patient completed at least one induction cycle. DVT developed in 14 of 50 patients (28%) randomly assigned to receive **thalidomide** but in only 2 of 50 patients (4%) not given the agent (P = .002). All episodes of DVT occurred during the first 3 cycles of induction. Administration of **thalidomide** was resumed safely in 75% of patients receiving anticoagulation therapy. Thus, **thalidomide** given in combination with multiagent chemotherapy and dexamethasone is assocd. with a significantly increased risk of DVT, which appears to be safely treated with anticoagulation and does not necessarily warrant discontinuation of **thalidomide**.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 10 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2001:682526 CAPLUS
DN 136:56
TI Management of small cell lung cancer
AU Yip, Desmond; Karapetis, Christos; Steel, Christopher
CS Medical Oncology Unit, The Canberra Hospital, Garran, ACT 2605, Australia
SO Expert Review of Anticancer Therapy (2001), 1(2), 197-210
CODEN: ERATBJ; ISSN: 1473-7140
PB Future Drugs Ltd.
DT Journal; General Review
LA English
AB A review with refs. Small cell lung cancer is a tumor that has a very

poor prognosis without treatment. It is however, highly responsive to chemotherapy and radiotherapy. Pretreatment clin. and lab. parameters - in addn. to staging - can prognosticate outcome and help define the aim of treatment. Different schedules of chemotherapy have been developed and varied strategies, such as chemotherapy dose intensification have been tried to improve outcomes. New agents, such as irinotecan, **gemcitabine** and topotecan have also been tested. Clin. trials have helped to define strategies of integrating thoracic radiotherapy and prophylactic cranial radiotherapy into management of those patients with limited disease to improve survival further. Despite good initial responses to treatment, most patients eventually relapse. Maintenance strategies with ongoing chemotherapy or novel agents, such as interferon, matrix metalloproteinase inhibitors, **thalidomide** and vaccines are discussed.

RE.CNT 117 THERE ARE 117 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 11 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 2001:350245 CAPLUS
DN 135:220491
TI High-dose therapy and innovative approaches to treatment of multiple myeloma
AU Barlogie, Bart
CS Arkansas Cancer Research Center, Little Rock, AR, 72205, USA
SO Seminars in Hematology (2001), 38(2, Suppl. 3), 21-27
CODEN: SEHEA3; ISSN: 0037-1963
PB W. B. Saunders Co.
DT Journal; General Review
LA English
AB A review with 9 refs. High-dose therapy in multiple myeloma (MM) appears to be superior in terms of event-free survival and overall survival compared with conventional therapy. Melphalan-based high-dose therapy increases complete remission rates from 5% to 50% and extends event-free survival beyond 3 yr and overall survival beyond 6 yr. Crit. disease features assocd. with durable complete remission, event-free survival, and overall survival include the absence of chromosome 13 deletion, low .beta.2-microglobulin, and low C-reactive protein levels. Data on 1,000 patients enrolled in tandem high-dose trials show that chromosome 13 deletion is an important prognostic feature. The timely application of a second cycle of high-dose therapy extends event-free survival and overall survival markedly in MM patients with low .beta.2-microglobulin levels. Long-term results of the total therapy trial indicate that patients who do not have chromosome 13 deletions and present with low C-reactive protein and .beta.2-microglobulin levels have longer complete remissions than patients lacking these prognostic factors. **Thalidomide** shows clear evidence of antitumor activity possibly because of its antiangiogenic activity. Magnetic resonance imaging (MRI) indicates that bone marrow lesions become smaller or disappear while patients receive dexamethasone, cyclophosphamide, etoposide, and **cisplatin** (DCEP) consolidation chemotherapy and that patients who have a compete remission after diagnostic MRI have a superior event-free and overall survival than those who still have persistent MRI lesions. Prospective trials are underway to evaluate the effectiveness of consolidation therapy (total therapy II).

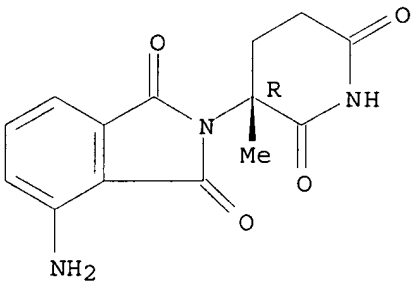
RE.CNT 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L1 ANSWER 12 OF 12 CAPLUS COPYRIGHT 2002 ACS
AN 1999:717767 CAPLUS
DN 131:317173
TI Novel approaches in myeloma therapy
AU Munshi, Nikhil C.; Barlogie, Bart; Desikan, K. Raman; Wilson, Carla
CS Department of Myeloma and Transplantation Research, University of Arkansas

for Medical Sciences, Little Rock, AR, 72205, USA
SO Seminars in Oncology (1999), 26(5, Suppl. 13), 28-34
CODEN: SOLGAV; ISSN: 0093-7754
PB W. B. Saunders Co.
DT Journal; General Review
LA English
AB A review, with 26 refs., discussing some of the current strategies that may improve the progression-free and overall survival of patients with multiple myeloma. High-dose melphalan (200 mg/m2) followed by .gtoreq.1 autologous peripheral blood stem cell transplantations is a safe and effective treatment regimen for multiple myeloma. This treatment regimen is as effective as std. therapy for myeloma in older (>65 yr) patients and in patients with renal failure. However, advanced age (>50 yr), duration of prior std. therapy (>12 mo), and a low CD34 mobilization potential (<20 .times. 106/kg) are assocd. with a higher incidence of cytogenetic myelodysplasia. Future efforts directed at curing multiple myeloma should incorporate the best remission-induction regimens presently available and should use consolidation/maintenance treatment (e.g., idiotype/dendritic cell vaccination and dexamethasone/cyclophosphamide/etoposide/ **cisplatin** combination chemotherapy) to enhance sustained complete remission. Other options to improve the treatment of myeloma include novel adjunctive therapies that target the myeloma cell microenvironment (e.g., bisphosphonates, **thalidomide**, other antiangiogenesis agents) and allogeneic transplantation techniques to induce a graft-vs.-myeloma effect.
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

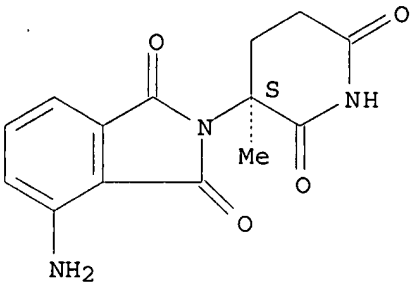
AN 1998:486299 CAPLUS
DN 129:216494
TI Tumor necrosis factor-alpha production enhancing activity of substituted 3'-methylthalidomide: influence of substituents at the phthaloyl moiety on the activity and stereoselectivity
AU Miyachi, Hiroyuki; Kolso, Yukiko; Shirai, Ryuichi; Niwayama, Satomi; Liu, Jun O.; Hashimoto, Yuichi
CS Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, 113-0032, Japan
SO Chemical & Pharmaceutical Bulletin (1998), 46(7), 1165-1168
CODEN: CPBTAL; ISSN: 0009-2363
PB Pharmaceutical Society of Japan
DT Journal
LA English
OS CASREACT 129:216494
AB The synthesis and tumor necrosis factor (TNF)-.alpha. prodn. enhancing activity of substituted 3'-methyl-thalidomides on human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate (TPA) was described. Though the introduction of an electron-donating amino group at the phthaloyl moiety of .alpha.-methylthalidomides enhanced the activity, substituted .alpha.-methylthalidomides showed decreased stereoselectivity as compared to that of non-substituted .alpha.-methylthalidomide. The data indicates that the TNF-.alpha. prodn. enhancing activity of thalidomide derivs. depends on both the electronic-state of substituents at the fused benzene ring and the stereochem. of the glutarimide moiety. (S)-4-amino-3'-methylthalidomide induced a 695% increase in the amt. of tumor necrosis factor-alpha prodn. at 0.3.mu.m by the human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate.
IT **212394-04-2P 212394-05-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tumor necrosis factor-alpha prodn. enhancing activity of substituted 3'-methylthalidomides)
RN 212394-04-2 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3R)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 212394-05-3 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-[(3S)-3-methyl-2,6-dioxo-3-piperidinyl]- (9CI) (CA INDEX NAME)

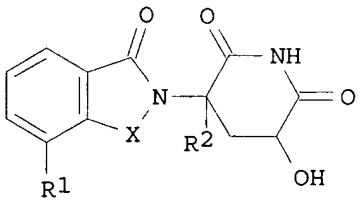
Absolute stereochemistry. Rotation (+).



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> d his

     (FILE 'HOME' ENTERED AT 17:14:40 ON 06 DEC 2002)

     FILE 'REGISTRY' ENTERED AT 17:14:53 ON 06 DEC 2002
L1                STRUC
L2             10 S L1
L3            175 S L1 FUL
L4                STRUC
L5            166 SEARCH L4 SSS  SUB=L3 FUL

     FILE 'CAPLUS' ENTERED AT 17:20:41 ON 06 DEC 2002
L6             17 S L5

     FILE 'REGISTRY' ENTERED AT 17:21:25 ON 06 DEC 2002
L7              9 S L3 NOT L5

     FILE 'CAPLUS' ENTERED AT 17:22:03 ON 06 DEC 2002
L8              8 S L7
```

```
=> s l5
L6          17 L5

=> d bib abs 1-17

L6   ANSWER 1 OF 17  CAPLUS  COPYRIGHT 2002 ACS
AN   2002:748793  CAPLUS
DN   137:247612
TI   Preparation of dioxopiperidinylisoindolin-1-ones and -isoindoline-1,3-
     diones for treatment of TNF.alpha.-mediated disease.
IN   Muller, George; Man, Hon-wah; Stirling, David I.
PA   USA
SO   U.S., 11 pp.
     CODEN: USXXAM
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------    ----  --------       ---------------  --------
PI   US 6458810          B1   20021001       US 2000-712550   20001114
     WO 2002094180       A2   20021128       WO 2001-US44107  20011114
         W:  AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE,
             ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS,
             LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,
             SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, TR
PRAI US 2000-712550    A    20001114
OS   MARPAT 137:247612
GI
```



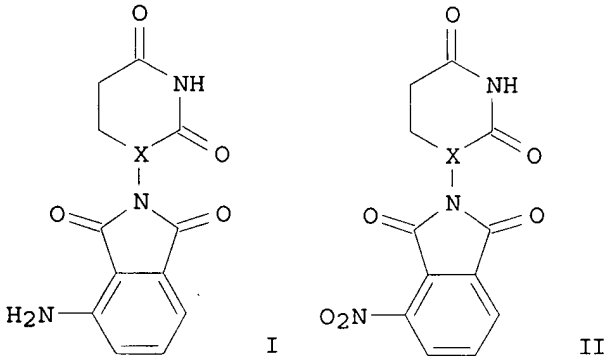
I

```
AB   Title compds. [I; X = CO, CH2; R1 = alkyl, NHR3; R2 = H, alkyl, halo; R3 =
     H, alkyl, cycloalkyl, (substituted) Ph, PhCH2, COR4; R4 = H, (substituted)
     alkyl, cycloalkyl, Ph, PhCH2], were prepd. as inhibitors of, and thus
     useful in the treatment of disease states mediated by, TNF.alpha. (no
     biol. or synthetic data).  I drug formulations are given.
RE.CNT  8     THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6   ANSWER 2 OF 17  CAPLUS  COPYRIGHT 2002 ACS
AN   2002:637473  CAPLUS
DN   137:185418
TI   Enantioselective preparation of 3-aminothalidomides for the treatment of
     diseases that are mediated by abnormal mitosis and/or angiogenesis
IN   Treston, Anthony; Shah, Jamshed H.; D'Amato, Robert J.; Hunsucker,
     Kimberly A.; Rougas, John; Conner, Barry P.; Pribluda, Victor; Swartz,
     Glenn M.
PA   The Children's Medical Center Corporation, USA
SO   PCT Int. Appl., 42 pp.
```

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002064083	A2	20020822	WO 2001-US45229	20011130

PI WO 2002064083 A2 20020822 WO 2001-US45229 20011130
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI US 2000-250219P P 20001130
GI



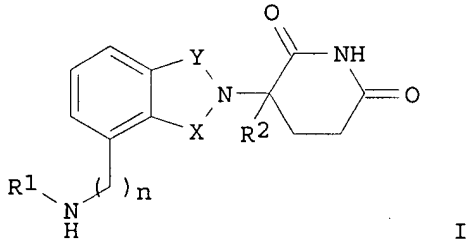
I II

AB Title compds. I [X = CH, (R)-enantiomer, (S)-enantiomer, (R,S) racemate] and their formulations were prepd. For example, condensation of (3S)-aminoglutarimide, e.g., prepd. from N-CBZ-L-glutamine in 2 steps, and 3-nitrophthalic anhydride provided nitrothalidomide II [X = CH, (S)-enantiomer], followed by nitro redn. afforded claimed aminothalidomide I [X = CH, (S)-enantiomer]. In vivo expts. in lung and plasma cell tumor metastatic tumor systems comparing the antitumor activity of the three enantiomeric prepns. of I, demonstrated the S-enantiomer to be the most active enantiomer in each tumor model. Compds. I are useful for the treatment of angiogenesis-assocd. diseases, e.g., cancer and macular degeneration.

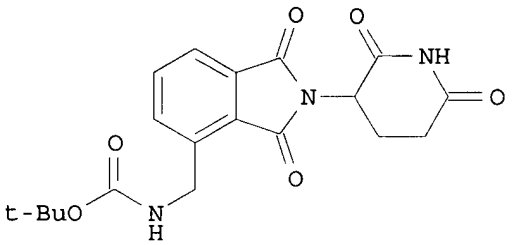
L6 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 2002:575064 CAPLUS
DN 137:125091
TI Preparation of 2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-diones, related compounds, and compositions thereof as TNF-.alpha. inhibitors for treatment of cancer, inflammatory disorders, heart disease, and related disorders
IN Robarge, Michael J.; Chen, Roger Shen-Chu; Muller, George W.; Man, Hon-Wah
PA Celgene Corporation, USA
SO PCT Int. Appl., 224 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	WO 2002059106			A1	20020801				WO 2001-US50401				20011221		
	W:	AE,	AG,	AL,	AM,	AT,	AU,	AZ,	BA,	BB,	BG,	BR,	BY,	BZ,	CA,	CH,	CN,
		CO,	CR,	CU,	CZ,	DE,	DK,	DM,	DZ,	EC,	EE,	ES,	FI,	GB,	GD,	GE,	GH,
		GM,	HR,	HU,	ID,	IL,	IN,	IS,	JP,	KE,	KG,	KP,	KR,	KZ,	LC,	LK,	LR,
		LS,	LT,	LU,	LV,	MA,	MD,	MG,	MK,	MN,	MW,	MX,	MZ,	NO,	NZ,	OM,	PH,
		PL,	PT,	RO,	RU,	SD,	SE,	SG,	SI,	SK,	SL,	TJ,	TM,	TR,	TT,	TZ,	UA,
		UG,	US,	UZ,	VN,	YU,	ZA,	ZW,	AM,	AZ,	BY,	KG,	KZ,	MD,	RU,	TJ,	TM
	RW:	GH,	GM,	KE,	LS,	MW,	MZ,	SD,	SL,	SZ,	TZ,	UG,	ZM,	ZW,	AT,	BE,	CH,
		CY,	DE,	DK,	ES,	FI,	FR,	GB,	GR,	IE,	IT,	LU,	MC,	NL,	PT,	SE,	TR,
		BF,	BJ,	CF,	CG,	CI,	CM,	GA,	GN,	GQ,	GW,	ML,	MR,	NE,	SN,	TD,	TG
PRAI	US 2000-258372P			P	20001227												
	US 2001-972487			A	20011005												
OS	MARPAT 137:125091																
GI																	



I



II

AB Title isoindole-imides I [wherein one of X and Y is CO and the other is CH2 or CO; R1 = H, (cyclo)alkyl, alkenyl, alkynyl, benzyl, aryl, alkylheterocycloalkyl, alkylheteroaryl, COR3, CSR3, CO2R4, alkyl-(NR6)2, alkyl-OR5, alkyl-CO2R5, CONHR3, CSNHR3, CON(R3)2, CSN(R3)2, or alkyl-OCOR5; R2 = H, benzyl, alkyl, alkenyl, or alkynyl; R3 = independently (cyclo)alkyl, alkenyl, alkynyl, benzyl, aryl, alkylheterocycloalkyl, alkylheteroaryl, alkyl-N(R6)2, alkyl-OR5, alkyl-CO2R5, alkyl-OCOR5, or CO2R5; R4 = alkyl, alkenyl, alkynyl, alkyl-OR5, benzyl, aryl, alkylheterocycloalkyl, or alkylheteroaryl; R5 = alkyl, alkenyl, alkynyl, benzyl, aryl, or heteroaryl; R6 = independently H, alkyl, alkenyl, alkynyl, benzyl, (hetero)aryl, or alkyl-CO2R5; or R6 groups may join to form a heterocycloalkyl group; n = 0-1; with the proviso that when n = 0, R1 .noteq. H; or pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates, or mixts. of stereoisomers thereof] were prepd. for reducing the level of cytokines and their precursors in mammals. In particular, the invention pertains to isoindole-imide compds. that are potent inhibitors of the prodn. of TNF-.alpha. (no data). For example, Me 2-(methoxycarbonyl)-3-nitrobenzoate was hydrogenated with 10% Pd/C (87%). The amine was converted to the nitrile by diazonium salt formation effected by treatment with NaNO3 followed by cyanide formation using classic Sandmeyer procedure (65%). The nitrile was reduced with 10% Pd/C

in MeOH and aq. HCl under hydrogen to afford Me 3-aminomethyl-2-(methoxycarbonyl)benzoate.bul.HCl (90%), which was treated with TEA and then reacted with di-t-Bu dicarbonate to give the carbamate (93%). Cyclization with 3-aminoglutarimide.bul.HCl using diisopropylethylamine in DMF produced II (82%). The 2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-diones and pharmaceutical compns. comprising them are useful for treating or preventing diseases or disorders in mammals, e.g. cancers, such as solid tumors and blood-born tumors; heart disease, such as congestive heart failure; osteoporosis; and genetic, inflammatory, allergic, and autoimmune diseases (no data).

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 2002:414530 CAPLUS
TI Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis
AU Tsenova, Liana; Mangaliso, Bande; Muller, George; Chen, Yong; Freedman, Victoria H.; Stirling, David; Kaplan, Gilla
CS Laboratory of Cellular Physiology and Immunology, The Rockefeller University, New York, NY, 10021, USA
SO Antimicrobial Agents and Chemotherapy (2002), 46(6), 1887-1895
CODEN: AMACCQ; ISSN: 0066-4804
PB American Society for Microbiology
DT Journal
LA English
AB Tuberculous meningitis (TBM), the most severe form of Mycobacterium tuberculosis infection in humans, is assocd. with significant morbidity and mortality despite successful treatment with antituberculous drugs. This is due to the irreversible brain damage subsequent to the local inflammatory response of the host to M. tuberculosis. Corticosteroids have been used in conjunction with antituberculous therapy in an attempt to modulate the inflammatory response, but this strategy has been of limited success. Therefore, we examd. whether combining antituberculous drugs with the immunomodulatory drug thalidomide or with a new thalidomide analog, immunomodulatory drug 3 (IMiD3), would be effective in reducing morbidity and mortality in an exptl. rabbit model of TBM. Intracisternal inoculation of 5.times.104 CFU of Mycobacterium bovis Ravenel in rabbits induced progressive subacute meningitis characterized by high cerebrospinal fluid (CSF) leukocytosis, protein influx, release of tumor necrosis factor (TNF), substantial meningeal inflammation, and mortality by day 28. Treatment with antituberculous drugs or with antituberculous drugs plus thalidomide improved the clin. course of disease somewhat and increased survival to about 50%. In contrast, treatment with antituberculous drugs in combination with IMiD3 limited pathol. neurol. changes and resulted in marked improvement (73%) in survival. IMiD3 treatment was also assocd. with reduced leukocytosis in the CSF and significantly lower levels of TNF in CSF and plasma. Histol., the meningeal inflammation in animals treated with antituberculous drugs plus IMiD3 was considerably attenuated compared to that of the other treatment groups. These results suggest a potential role for IMiD3 in the management of TBM in patients.

RE.CNT 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 2002:323075 CAPLUS
DN 137:241801
TI S-3-amino-phthalimido-glutarimide inhibits angiogenesis and growth of B-cell neoplasias in mice
AU Lentzsch, Suzanne; Rogers, Michael S.; LeBlanc, Richard; Birsner, Amy E.; Shah, Jamshed H.; Treston, Anthony M.; Anderson, Kenneth C.; D'Amato, Robert J.

CS Jerome Lipper Multiple Myeloma Center, Department of Adult Oncology, Dana-Farber Cancer Institute and Department of Medicine, Harvard Medical School, Boston, MA, 02115, USA
SO Cancer Research (2002), 62(8), 2300-2305
CODEN: CNREA8; ISSN: 0008-5472
PB American Association for Cancer Research
DT Journal
LA English
AB Thalidomide has recently been shown to be useful in the treatment of multiple myeloma and may also be useful in the treatment of other hematol. malignancies. We have identified a new deriv. of thalidomide, S-3-[3-amino-phthalimido]-glutarimide (S-3APG) with dual activity against B-cell neoplasias. S-3APG was able to directly inhibit the proliferation of myeloma and Burkitt's lymphoma cell lines in vitro without showing toxicity to normal bone marrow stromal cells or hematopoietic progenitor cells. In vivo, S-3APG treatment of drug resistant myeloma cell tumors in mice was able to produce complete and sustained regressions without any obsd. toxicity. Addnl., S-3APG induced complete regressions of Burkitt's lymphoma cell tumors. Furthermore, S-3APG inhibited angiogenesis more potently than thalidomide in the murine corneal micropocket model. We conclude that S-3APG is a powerful anti-myeloma and anti-B-cell-lymphoma agent that has both anti-proliferative and antiangiogenic effects.
RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 2002:211227 CAPLUS
DN 137:241664
TI Thalidomide and its analogues as cyclooxygenase inhibitors
AU Noguchi, Tomomi; Shimazawa, Rumiko; Nagasawa, Kazuo; Hashimoto, Yuichi
CS Institute of Molecular & Cellular Biosciences, The University of Tokyo, Bunkyo-ku, Tokyo, 113-0032, Japan
SO Bioorganic & Medicinal Chemistry Letters (2002), 12(7), 1043-1046
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English
AB Thalidomide showed cyclooxygenase (COX)-1/2 inhibitory activity with a potency comparable to that of aspirin. Structural development studies of thalidomide resulted in potent COX-1/2 inhibitors, and COX-1-selective and COX-2-selective inhibitors.
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 2002:38054 CAPLUS
DN 136:256585
TI Mechanism of action of thalidomide and 3-aminothalidomide in multiple myeloma
AU D'Amato, Robert J.; Lentzsch, Suzanne; Anderson, Kenneth C.; Rogers, Michael S.
CS Children's Hospital and the Dana Farber Cancer Institute, Boston, MA, USA
SO Seminars in Oncology (2001), 28(6), 597-601
CODEN: SOLGAV; ISSN: 0093-7754
PB W. B. Saunders Co.
DT Journal; General Review
LA English
AB A review. We have explored the mechanism of the antiangiogenic effects of thalidomide by structure-activity studies. These investigations revealed that angiogenesis inhibition correlates with teratogenicity but not with tumor necrosis factor-alpha inhibition. Addnl., one analog of thalidomide, 3-aminothalidomide, exhibited an unusual capacity to directly inhibit myeloma cell proliferation. This activity did not correlate with

TNF-.alpha. inhibition. Thus 3-aminothalidomide was found to inhibit multiple myeloma through effects on both the tumor and vascular compartment. The effects of an inhibitor of both the tumor and vascular compartments of a tumor on tumor growth may be synergistic.

RE.CNT 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 2001:452859 CAPLUS
DN 135:51096
TI Compositions for the prevention and treatment of atherosclerosis and restenosis
IN Zeldis, Jerome B.
PA Celgene Corp., USA
SO PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2001043743	A1	20010621	WO 2000-US33708	20001213
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002054899	A1	20020509	US 2000-734460	20001211
EP 1242082	A1	20020925	EP 2000-984269	20001213
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRAI US 1999-170820P	P	19991215		
WO 2000-US33708	W	20001213		

AB Methods and compns. for the prevention and treatment of all forms of atherosclerosis are described. Administration of compds. such as thalidomide, its analogs, hydrolysis products, metabolites, derivs. and precursors as well as addnl. compds. capable of inhibiting tumor necrosis factor-.alpha. (TNF-.alpha.) are used in the invention. Also disclosed is the coating of prosthetic devices, such as stents, with the compds. of the invention for the prevention and/or treatment of restenosis. Tablets contained 1-oxo-2-(2,6-dioxopiperidin-3-yl)-4-aminoisoindoline 50.0, lactose 50.7, wheat starch 7.5, PEG-6000 5.0, talc 5.0, and Mg stearate 1.8 and water qs.

RE.CNT 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

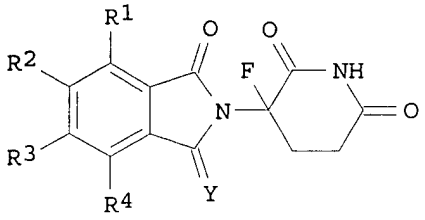
L6 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 1999:603139 CAPLUS
DN 131:214197
TI Preparation of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines for reducing inflammatory cytokine levels.
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu; Man, Hon-wah
PA Celgene Corp., USA
SO U.S., 12 pp., Cont. -in-part of U. S. 5,874,448.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	US 5955476	A	19990921	US 1998-42274	19980313
	US 5874448	A	19990223	US 1997-976140	19971118
	CA 2317834	AA	19990916	CA 1998-2317834	19981117
	WO 9946258	A1	19990916	WO 1998-US24453	19981117
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	AU 9914138	A1	19990927	AU 1999-14138	19981117
	AU 752958	B2	20021003		
	EP 1062214	A1	20001227	EP 1998-958016	19981117
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002506068	T2	20020226	JP 2000-535637	19981117
	BR 9815613	A	20020528	BR 1998-15613	19981117
	NO 2000002529	A	20000630	NO 2000-2529	20000516
	FI 2000001192	A	20000714	FI 2000-1192	20000518
PRAI	US 1997-976140	A2	19971118		
	US 1998-42274	A	19980313		
	WO 1998-US24453	W	19981117		

OS MARPAT 131:214197

GI



I

AB Title compds. (I; Y = O, H2; R1-R4 = H, halo, alkyl, alkoxy, amino), were prepd. for redn. of tumor necrosis factor and interleukin levels (no data). Thus, a soln. of 1,3-dioxo-2-(1-tert-butoxycarbonyl-2,6-dioxopiperidin-3-yl)isoindoline (prepn. given) in THF at -40.degree. was treated with Li[N(SiMe3)]2 soln. and then with N-fluorobenzenesulfonimide followed by stirring overnight to give 10% 1,3-dioxo-2-(1-tert-butoxycarbonyl-2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline. The latter was stirred with HCl in dioxane for 3 days to give 77% 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline. Drug formulations contg. the latter are given.

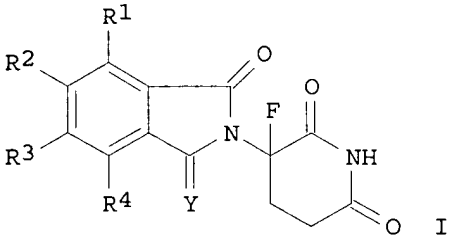
RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 10 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 1999:595162 CAPLUS
DN 131:228653
TI Preparation of 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and their use to reduce tumor necrosis factor .alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu; Man, Hon-wah
PA Celgene Corporation, USA
SO PCT Int. Appl., 32 pp.
CODEN: PIXXD2
DT Patent

LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9946258	A1	19990916	WO 1998-US24453	19981117
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	US 5955476	A	19990921	US 1998-42274	19980313
	CA 2317834	AA	19990916	CA 1998-2317834	19981117
	AU 9914138	A1	19990927	AU 1999-14138	19981117
	AU 752958	B2	20021003		
	EP 1062214	A1	20001227	EP 1998-958016	19981117
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002506068	T2	20020226	JP 2000-535637	19981117
	BR 9815613	A	20020528	BR 1998-15613	19981117
	NO 2000002529	A	20000630	NO 2000-2529	20000516
	FI 2000001192	A	20000714	FI 2000-1192	20000518
PRAI	US 1998-42274	A	19980313		
	US 1997-976140	A2	19971118		
	WO 1998-US24453	W	19981117		

OS MARPAT 131:228653
GI



I

AB 1-Oxo- and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines (I; R1-R4 = H, halo, C1-4 alkyl, C1-4 alkoxy, amino; Y = O, H2) and their acid addn. salts reduce the levels of inflammatory cytokines, e.g., TNF-.alpha. in mammals (no data). A typical embodiment is 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline which was prepd. by N-protection of 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)isoindoline with (Me3CO2C)2O (90%), fluorination of N-BOC-protected intermediate with (PhSO2)2NF in presence of BuLi or (Me3Si)2NLi (10%), and deprotection with HCl (dioxane soln.) (77% yield). Tablets, capsules and injection or infusion solns. contg. I are formulated.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 1999:386135 CAPLUS
DN 131:129881
TI Amino-substituted thalidomide analogs: potent inhibitors of TNF-.alpha. production
AU Muller, George W.; Chen, Roger; Huang, Shaei-Yun; Corral, Laura G.; Wong, Lu Min; Patterson, Rebecca T.; Chen, Yuxi; Kaplan, Gilla; Stirling, David

I.

CS Celgene Corporation, Warren, NJ, 07059, USA

SO Bioorganic & Medicinal Chemistry Letters (1999), 9(11), 1625-1630
CODEN: BMCLE8; ISSN: 0960-894X
PB Elsevier Science Ltd.
DT Journal
LA English

AB Thalidomide is a known inhibitor of TNF-.alpha. release in LPS stimulated human PBMC. Herein we describe the TNF-.alpha. inhibitory activity of amino substituted analogs of thalidomide and its isoindolin-1-one analog, EM-12. The 4-amino substituted analogs were found to be potent inhibitors of TNF-.alpha. release in LPS stimulated human PBMC.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 12 OF 17 CAPLUS COPYRIGHT 2002 ACS

AN 1999:136769 CAPLUS
DN 130:168244

TI Substituted 2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and method of reducing TNF.alpha. levels

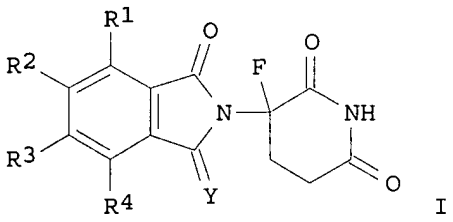
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-Chu; Man, Hon-Wah
PA Celgene Corporation, USA

SO U.S., 10 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5874448	A	19990223	US 1997-976140	19971118
	US 5955476	A	19990921	US 1998-42274	19980313
	NO 2000002529	A	20000630	NO 2000-2529	20000516
	FI 2000001192	A	20000714	FI 2000-1192	20000518
PRAI	US 1997-976140	A2	19971118		
	US 1998-42274	A	19980313		
	WO 1998-US24453	W	19981117		

OS MARPAT 130:168244

GI



I

AB 1-Oxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines and 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindolines reduce the levels of TNF.alpha. in mammals (no data), and may be useful in the treatment of viral infections. The compds. I [Y = O or H2; R1, R2, R3, and R4 = H, halo, C1-4 alkyl or alkoxy, or amino], and their acid addn. salts when a protonatable N atom is present, are claimed. A typical embodiment is 1,3-dioxo-2-(2,6-dioxo-3-fluoropiperidin-3-yl)isoindoline (II), i.e. I [Y = O, R1-R4 = H]. This compd. was prepd. in a variety of ways. For instance, the non-fluorinated analog of II was N-BOC-protected on its piperidine ring, lithiated with BuLi in THF, fluorinated with N-fluorobenzenesulfonimide, and deprotected with HCl, to give II.

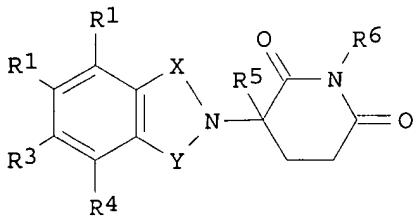
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 13 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 1998:795004 CAPLUS
DN 130:38290
TI Substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and 1-oxoisoindolines and method of reducing tnf.alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu
PA Celgene Corporation, USA
SO PCT Int. Appl., 31 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9854170	A1	19981203	WO 1998-US10886	19980528
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9877012	A1	19981230	AU 1998-77012	19980528
	AU 741982	B2	20011213		
	EP 984955	A1	20000315	EP 1998-924959	19980528
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2002501536	T2	20020115	JP 1999-500909	19980528
	FI 9902490	A	20000127	FI 1999-2490	19991123
	NO 9905751	A	20000128	NO 1999-5751	19991123
	US 6395754	B1	20020528	US 2000-445002	20000222
	US 2002173658	A1	20021121	US 2002-143416	20020510
PRAI	US 1997-48278P	P	19970530		
	WO 1998-US10886	W	19980528		
	US 2000-445002	A1	20000222		

OS MARPAT 130:38290
GI



I

AB Substituted 2-(2,6-dioxopiperidin-3-yl)phthalimides and 1-oxo-2-(2,6-dioxopiperidin-3-yl)isoindolines (I) (one of X and Y = CO and the other is CH2 or CO; R1, R2, R3, R4 independently is halo, C1-4-alkyl or -alkoxy or one of R1, R2, R3, R4 is (un)substituted NH2 and the others are H; R5 = H or C1-8-alkyl, benzo, Cl, F; R6 = substituted CH2O(CO)R8CH2NH2 (R8 = m- or p-phenylene of (CH2)n (n = 1-4))) were claimed to reduce the levels of TNF.alpha. in a mammal. I (R6 = H) were prepd. and used in pharmaceutical compns. Thus 1-oxo-2-(2,6-dioxo-3-methylpiperidin-3-yl)-4,5,6,7-tetrafluoroisoindoline was prepd. in a multistep reaction initially from methylglutamic acid which was converted

via many steps to .alpha.-amino-.alpha.-methylglutarimide which was converted visa many steps to the final product.
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 1998:486299 CAPLUS
DN 129:216494
TI Tumor necrosis factor-alpha production enhancing activity of substituted 3'-methylthalidomide: influence of substituents at the phthaloyl moiety on the activity and stereoselectivity
AU Miyachi, Hiroyuki; Kolso, Yukiko; Shirai, Ryuichi; Niwayama, Satomi; Liu, Jun O.; Hashimoto, Yuichi
CS Institute of Molecular and Cellular Biosciences, The University of Tokyo, Tokyo, 113-0032, Japan
SO Chemical & Pharmaceutical Bulletin (1998), 46(7), 1165-1168
CODEN: CPBTAL; ISSN: 0009-2363
PB Pharmaceutical Society of Japan
DT Journal
LA English
OS CASREACT 129:216494
AB The synthesis and tumor necrosis factor (TNF)-.alpha. prodn. enhancing activity of substituted 3'-methyl-thalidomides on human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate (TPA) was described. Though the introduction of an electron-donating amino group at the phthaloyl moiety of .alpha.-methylthalidomides enhanced the activity, substituted .alpha.-methylthalidomides showed decreased stereoselectivity as compared to that of non-substituted .alpha.-methylthalidomide. The data indicates that the TNF-.alpha. prodn. enhancing activity of thalidomide derivs. depends on both the electronic-state of substituents at the fused benzene ring and the stereochem. of the glutarimide moiety. (S)-4-amino-3'-methylthalidomide induced a 695% increase in the amt. of tumor necrosis factor-alpha prodn. at 0.3.mu.m by the human leukemia cell line HL-60 stimulated with 12-O-tetradecanoyl-phorbol 13-acetate.
RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

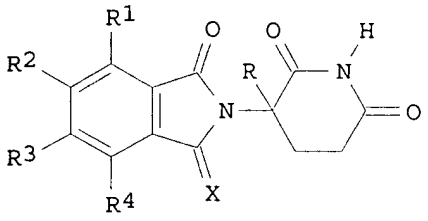
L6 ANSWER 15 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 1998:87727 CAPLUS
DN 128:140615
TI Substituted 2-(2,6-dioxo-3-piperidinyl)phthalimides and -1-oxoisoindolines and method of reducing TNF-.alpha. levels
IN Muller, George W.; Stirling, David I.; Chen, Roger Shen-chu
PA Celgene Corp., USA; Muller, George W.; Stirling, David I.; Chen, Roger Shen-Chu
SO PCT Int. Appl., 48 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 7

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9803502	A1	19980129	WO 1997-US13375	19970724
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5635517	A	19970603	US 1996-690258	19960724
US 5635517	B1	19990629		

	US 5798368	A	19980825	US 1996-701494	19960822
	AU 9738998	A1	19980210	AU 1997-38998	19970724
	AU 715779	B2	20000210		
	EP 925294	A1	19990630	EP 1997-936295	19970724
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	JP 2001503384	T2	20010313	JP 1998-507259	19970724
	RU 2177944	C2	20020110	RU 1999-103124	19970724
	FI 9900101	A	19990319	FI 1999-101	19990119
	US 6281230	B1	20010828	US 2000-543809	20000406
	US 6476052	B1	20021105	US 2000-633908	20000807
	US 6316471	B1	20011113	US 2000-634061	20001017
	US 6335349	B1	20020101	US 2000-716528	20001120
	US 2002045643	A1	20020418	US 2001-781179	20010212
	US 2002183360	A1	20021205	US 2002-119486	20020410
PRAI	US 1996-690258	A	19960724		
	US 1996-701494	A	19960822		
	WO 1994-US7411	A	19940701		
	US 1996-701499	A1	19960724		
	US 1997-48278P	P	19970530		
	WO 1997-US13375	W	19970724		
	US 1999-230389	B3	19990507		
	US 2000-543804	A3	20000406		
	US 2000-543809	A1	20000406		
	US 2000-633908	A1	20000807		

OS MARPAT 128:140615

GI



I

AB Title compds. I (X = O, H2; R = H, alkyl, benzyl, halo; R1, R2, R3, R4 = H, alkyl, alkoxy, halo, amino) were prepd. for TNF-.alpha. redn. in mammals. Thus, I (X = O, R = R1 = R3 = R4 = H, R2 = NO2), prepd. from 4-nitrophthalic anhydride and .alpha.-aminoglutarimide hydrochloride, was hydrogenated over 10% Pd/C in 1,4-dioxane at 50 psi for 6.5 h to give 69% I (X = O, R = R1 = R3 = R4 = H, R2 = NH2). Several examples of formulations were given.

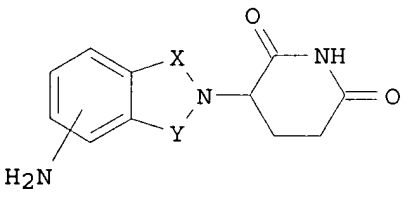
L6 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2002 ACS
AN 1997:375290 CAPLUS
DN 127:86110
TI Method of reducing TNF.alpha. levels with amino-substituted 2-(2,6-dioxopiperidin-3-yl)-1-oxo- and 1,3-dioxoisoindolines
IN Muller, George W.; Stirling, David I.; Chen, Roger S. -c
PA Celgene Corp., USA
SO U.S., 7 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 7

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	US 5635517	A	19970603	US 1996-690258	19960724
	US 5635517	B1	19990629		
	CA 2261762	AA	19980129	CA 1997-2261762	19970724
	WO 9803502	A1	19980129	WO 1997-US13375	19970724
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9738998	A1	19980210	AU 1997-38998	19970724
	AU 715779	B2	20000210		
	EP 925294	A1	19990630	EP 1997-936295	19970724
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	CN 1239959	A	19991229	CN 1997-180299	19970724
	JP 2001503384	T2	20010313	JP 1998-507259	19970724
	RU 2177944	C2	20020110	RU 1999-103124	19970724
	FI 9900101	A	19990319	FI 1999-101	19990119
	US 6281230	B1	20010828	US 2000-543809	20000406
	US 6476052	B1	20021105	US 2000-633908	20000807
	US 6316471	B1	20011113	US 2000-634061	20001017
	US 6335349	B1	20020101	US 2000-716528	20001120
	US 2002045643	A1	20020418	US 2001-781179	20010212
PRAI	WO 1994-US7411	A	19940701		
	US 1996-690258	A	19960724		
	US 1996-701499	A1	19960724		
	US 1996-701494	A	19960822		
	US 1997-48278P	P	19970530		
	WO 1997-US13375	W	19970724		
	US 1999-230389	B3	19990507		
	US 2000-543804	A3	20000406		
	US 2000-543809	A1	20000406		

OS MARPAT 127:86110

GI



I

AB 1-Oxo- and 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)isoindolines (I; 1 of X, Y = C:O; other of X, Y = C:O, CH2) substituted with amino in the benzo ring are prepd. which reduce the levels of TNF.alpha. in a mammal. I are therefore useful in treatment of inflammatory, infectious, immunol., or malignant diseases. Thus, 1,3-dioxo-2-(2,6-dioxopiperidin-3-yl)-5-aminoisoindoline (II) was prepd. by catalytic hydrogenation of the corresponding 5-nitro compd. (prepd. from 4-nitrophthalic anhydride and .alpha.-aminoglutarimide-HCl) over Pd/C. Tablets each contg. 50 mg II were prepd. from a mixt. of II 50.0, lactose 50.7, wheat starch 7.5, PEG-6000 5.0, talc 5.0, Mg stearate 1.8 g, and sufficient water for granulation.

L6 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2002 ACS

AN 1968:76672 CAPLUS
DN 68:76672
TI Relation between the chemical structure and embryotoxic activity of thalidomide and related compounds
AU Smith, Robert Leslie; Fabro, Sergio; Schumacher, Herbert; Williams, Richard Tecwyn
CS St. Mary's Hosp. Med. School, Paddington, Engl.
SO Symp. Embryopathic Act. Drugs (1965), 194-209
CODEN: 19CSAC
DT Conference
LA English
AB The embryopathic properties in the rabbit of a no. of compds. chem. related to thalidomide (I) were investigated in an attempt to assess those structural features of I that were important for its teratogenic activity. A relation between the structure and embryotoxic properties of I, and related compounds was observed. Administration of I had a clear and consistent embryotoxic effect. The embryotoxic properties of I did not appear to be due to the simple chem. units such as phthalimide, phthalic acid, 3-aminoglutarimide and L- and D- glutamine whose structures are present in I. The phthalimide group of I was important for embryotoxic activity. The structural requirements for N substituent were not clear. A no. of N-substituted phthalimides (II) appeared to be devoid of significant embryopathic properties. The most effective group for inducing high embryotoxic activity was 3-glutarimide as present in I. The possibility of a no. of factors influencing the embryotoxic activity of II is discussed. The embryotoxic activity of I may stem from the marked reactivity of its phthalimide group, which may be involved in acylating some components of the embryonic structure.

=> d hitstr 17

L6 ANSWER 17 OF 17 CAPLUS COPYRIGHT 2002 ACS
IT **19171-19-8**
RL: BIOL (Biological study)
(teratogenic activity of)
RN 19171-19-8 CAPLUS
CN 1H-Isoindole-1,3(2H)-dione, 4-amino-2-(2,6-dioxo-3-piperidinyl)- (9CI) (CA INDEX NAME)